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SYNTHESIS AND PROPERTIES OF SYMMETRICAL AND ASYMMETRICAL PHTHALOCYANINES WITH *D,L*-LEUCINE FRAGMENTS

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Nucleophilic substitution of the nitro group in 4-nitrophthalocyanine by the D,L-leucine fragment yields N-(3,4-dicyanophenyl)-D,L-leucine possessing a chiral site. This product was used to synthesize new symmetrical and asymmetrical phthalocyanines.

Keywords: N-(3,4-dicyanophenyl)-*D,L*-leucine, *D,L*-leucine, phthalocyanine.

The synthesis and study of phthalocyanines possessing an 18π-electron macrosystem and displaying unique properties is a rapidly developing field in the chemistry of macroheterocyclic compounds.

Promising research in this field involves the synthesis of asymmetrically substituted phthalocyanines and study of these compounds for application in nonlinear optics, thin-film electronics, and liquid crystals [1-8]. There is no information in the literature on the synthesis and properties of phthalocyanines containing covalently bonded residues of natural products, especially, amino acids. A nonconventional approach to deciphering DNA sequences involves use of porphyrins modified with a short peptide chain specific for precisely determined sites in the intercalation region as anchor structures [9]. Thus, for example, leucine and isoleucine can bind by means of van der Waals forces to the methyl group of thymine [10]. All amino acids can bind nonspecifically by means of ionic interactions with the frame of the DNA molecule. On the other hand, porphyrins with amino acid residues have been studied extensively for use in photodynamic cancer therapy [11] as in model systems with intermolecular electron transfer [12].

N-(3,4-Dicyanophenyl)-*D,L*-leucine (**1**) was used to synthesize 4-(N-*D,L*-leucyl)-8,11,15,18,22,25-hexa(pentyloxy)phthalocyanine (**2**) of the A_3B type where A is an isoindole fragment with two OC_5H_{11} fragments and B is an analogous fragment with substituent X and the nickel complex of tetra-(N-*D,L*-leucyl)phthalocyanine (**3**). Starting dinitrile **1** was obtained by the nucleophilic substitution of the nitro group in 4-nitrophthalonitrile (**4**) upon the reaction of this nitro derivative with *D,L*-leucine in DMF in the presence of freshly roasted potassium carbonate (Scheme 1). Dinitrile **1** was purified by column chromatography. The composition and structure of this product were supported by elemental analysis and IR spectroscopy.

The IR spectra of **1** were taken for KBr pellets and nujol suspensions, which permitted reliable determination of the stretching bands of the various bonds and the groups participating in intermolecular hydrogen bonding characteristic for amino acids. We should note that, in comparison with the spectra of nitrophthalodinitrile **4**, the spectra of dinitrile **1** lack bands corresponding to asymmetric and symmetric

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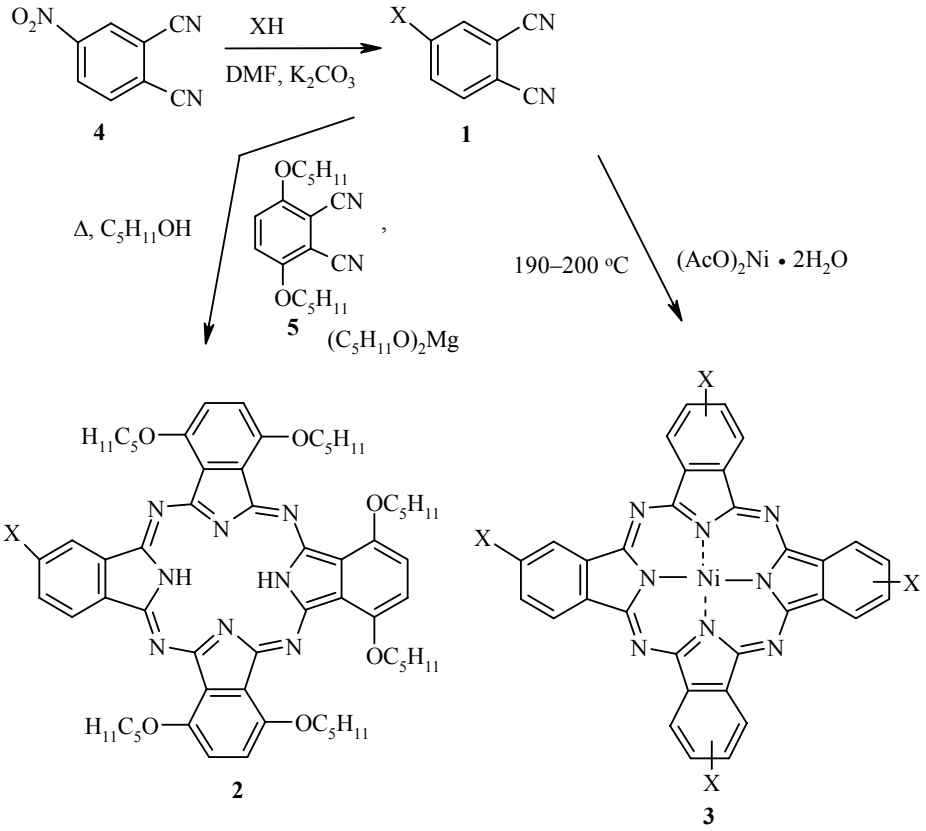
Scheme 1



X = *D*,*L*-NHCH(COOH)–Bu-*i*

stretching of the N=O bonds (at 1540 and 1336 cm^{-1}) but display the νC≡N band at 2224 cm^{-1}. The spectra of **1** also have a series of new bands, primarily, a band at 1718 cm^{-1} corresponding to stretching of the carboxyl C=O bond and also bands at 3460 and 3320 cm^{-1} (in the spectrum of the nujol suspension) for stretching of the amino acid O–H and N–H fragments. The broadening and displacement of these bands toward lower frequencies indicates the participation of these groups in intermolecular hydrogen bonding [13]. Furthermore, new bands are found in the spectrum taken for a KBr pellet at 2960-2940 cm^{-1}, corresponding to stretching of aliphatic C–H fragments. The doublet at 1384 and 1320 cm^{-1} in this spectrum may be assigned to C–Me groups [13], while the band at 1350 cm^{-1} may be assigned to stretching of C–N bonds.

Phthalocyanine **2** was obtained by random condensation upon heating dinitrile **1** and 3,6-di(pentyloxy)phthalodinitrile (**5**) in 1:5 mole ratio with an excess of magnesium 1-pentylate in 1-pentanol at reflux (see Scheme 1). After demetalation by treatment with acetic acid, the phthalocyanines were separated by column chromatography. The already reported symmetrical octa(pentyloxy)phthalocyanine [14] was not formed, as shown by the results of a control experiment involving the heating of dinitrile **5** under the same conditions in the absence of **1**. A bright green zone was isolated when 1:1 benzene–$CHCl_3$ was used as the eluent. Thin-layer chromatography indicated that this zone consisted of two phthalocyanine products **2** and an unknown impurity. Phthalocyanine **2** was isolated as a pure sample upon recrystallization from DMF.

The structure of phthalocyanine **2** was indicated by its ^{1}H NMR spectrum in $CDCl_3$. The singlet for the CO_2H group proton is at lowest field (9.1 ppm). The aromatic protons appear as multiplets at 8.2-7.8 ppm (for three protons of fragment B) and 7.8-7.3 ppm (for six protons of fragments A). The signals of the CH_2 group protons are seen as four multiplets: at 4.8-4.6 ppm (four equivalent OCH_2 groups), 4.9-3.9 ppm (two CH_2 groups closest to fragment B), 3.7-3.4 ppm (CH_2 group of the amino acid residue), and 2.4-1.4 ppm (other CH_2 groups).

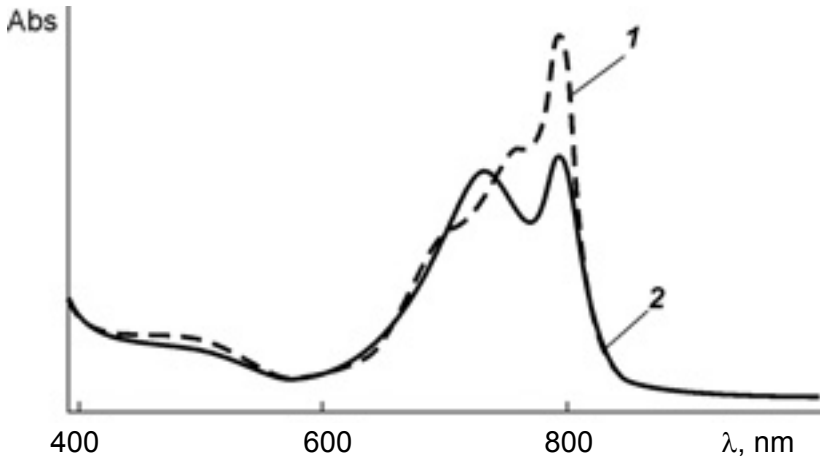


Fig. 1. Electronic absorption spectra of **2**: *1*) solution in $CHCl_3$ and *2*) same solution with added pyridine.

The amino acid CH protons and eight CH_3 groups are seen as a singlet at 3.1 ppm and multiplet at 1.2-0.7 ppm, respectively. The most significant differences are observed for the signals of the ring and amino acid NH protons. The ring NH protons are seen as a singlet shifted upfield (0.4 ppm) due to the shielding of the large ring. The amino acid NH group singlet is at much lower field (5.9 ppm), which, along with its broadened shape, indicates the participation of this group in hydrogen bonding.

The electronic absorption spectrum of phthalocyanine **2** (Fig. 1) has three bands, two of which appear as inflections (763 and 712 nm). These bands account specifically for the green color of solutions of **2**. The strongest band has a maximum at 790 nm, i.e., is found in the near-IR region. We should note that this band is shifted bathochromically by about 25 nm in comparison to the analogous band in the spectrum of the octa(pentyloxy)phthalocyanine reported by Dewar et al. [14] and dilute solutions of **2** do not obey the Lambert–Bouguer–Beer law. This finding along with the ^{1}H NMR spectral data indicate that phthalocyanine **2** is aggregated in solution due to intermolecular hydrogen bonding similar to starting dinitrile **1**. In this regard, we carried AM1 quantum chemical calculations for **1** with full optimization of all geometrical parameters. Figure 2 shows the PLUTO representation of the dimer form of dinitrile **1**.

Dimer **6** is formed due to two bridging N–H···O=C hydrogen bonds with length 2.17 Å. The O–H–N bond angles are 161.22 and 165.57°. The dimerization of **1** does not lead to a significant change in the geometry of this molecule but the hydrogen bonds are very strong, as found by comparing the enthalpies of formation of dinitrile **2** and dimer **6**. In the former case, ΔH^0_{298} = -10.82 kcal/mol, while, in the latter, ΔH^0_{298} = -37.78 kcal/mol. Thus, 8.48 kcal/mol are expended on the formation of each hydrogen bond. We might assume that such dimerization is also characteristic for phthalocyanine **2**. The following experiment was carried out to support this hypothesis. Salts are known to form upon the addition of bases such as pyridine to solutions of carboxylic acids, leading to destruction of the hydrogen bonds involving the carboxyl groups. This behavior would be expected for **2**. However, the addition of a small amount of pyridine to a chloroform solution of **2** led to a significant drop in the strength of the band at longest wavelength at 792 nm in the electronic spectrum of this compound with a concurrent increase in intensity of the band at 731 nm assigned to absorption of the associated form of phthalocyanine **2** [16] (see Fig. 1). In chloroform solution, phthalocyanine **2** probably tends to dimerize due to the formation of intermolecular hydrogen bonds involving the carboxyl groups of the amino acid residue. The addition of pyridine to this solution leads to a pyridinium salt, which, as indicated by the change in the spectral curves, has a greater tendency to undergo intermolecular interactions due to both an increase in the molecular dipole moment as a whole (dipole–dipole interaction) and the greater tendency of the salt to undergo ππ-interactions of macroaromatic ring.

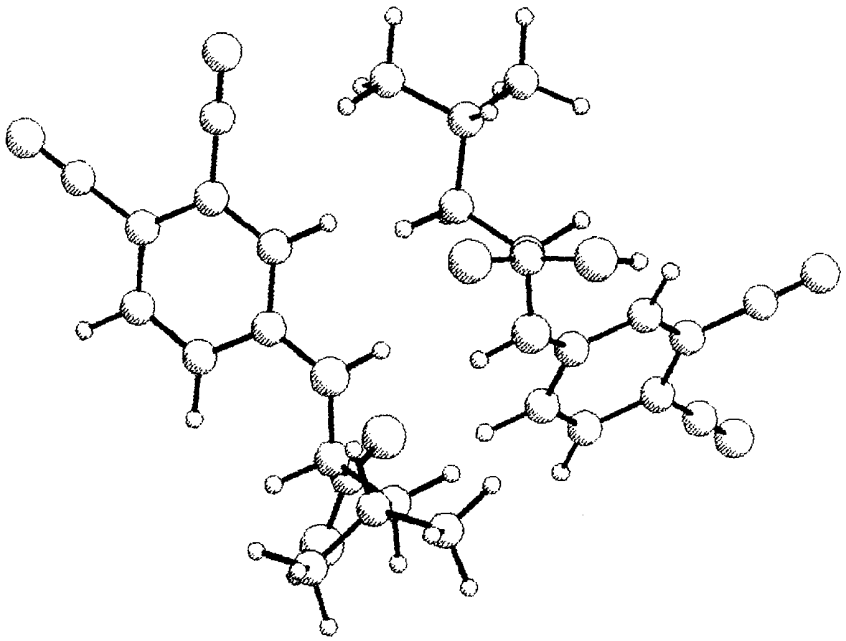


Fig. 2. PLUTO representation of dimer **6** of dinitrile **1** from an AM1 calculation.

The synthesis of phthalocyanine **3** was carried out by a reported procedure employing the reaction of dinitrile **1** with nickel diacetate dihydrate at 190-200°C, leading probably to formation of mixture of isomers differing in the position of the amino acid residue. Phthalocyanine **3** was purified by reprecipitation from sulfuric acid with subsequent washing with acetone in a Soxhlet apparatus. The composition and structure of this product were supported by elemental analysis and electronic spectroscopy. We should note that introduction of four amino acid fragments into the phthalocyanine molecule does not lead to a significant change in its spectrum. Two bands characteristic for the spectra of metal complexes of unsaturated phthalocyanine are seen in the electronic spectrum taken for a DMF solution. The position of the short-wavelength B-band (Soret band) at 334 nm is retained, while the long-wavelength Q-band, which is more sensitive to the nature of the substituents in the isoindole fragments of the macroheterocycle, is shifted bathochromically by 5 nm (maximum at 672 nm) and somewhat broadened, which indicates the existence of **3** as a mixture of isomers since band broadening is a characteristic of all tetrasubstituted phthalocyanines. Such a weak substituent effect on the electronic absorption spectra of phthalocyanine **3** results, in our view, from compensation of the electron-donor effect of the secondary amino group of the substituent by the electron-withdrawing effect of its carboxyl group and the substituent as a whole becomes electroneutral.

Thus, in the case of *D,L*-leucine, nucleophilic substitution of the nitro group in 4-nitrophthalonitrile by the amino acid residue yields new chiral derivatives, which may be used for the synthesis of symmetrical and asymmetrical phthalocyanines.

EXPERIMENTAL

The electronic absorption spectra of the products were taken on a Hitachi UV-2000 spectrometer and the ^{1}H NMR spectra were taken on a Bruker AM-200 spectrometer at 200 MHz.

Samples of phthalodinitriles **4** and **5** were prepared according to reported procedures [14, 17] and were identified by elemental analysis and comparison of their melting points with the reported data.

A sample of 2,3-dicyanohydroquinone, required for the preparation of dinitrile **5**, was obtained from Aldrich and used without further purification.

N-(3,4-Dicyanophenyl)-*D,L*-leucine (1). A sample of *D,L*-leucine (0.76 g, 5.8 mmol) and K_2CO_3 (0.5 g) were added to a solution of dinitrile **4** (1 g, 5.8 mmol) in DMF (20 ml) and heated at reflux for 4 h with stirring. After cooling, water (50 ml) was added and the mixture was extracted with two 20-ml chloroform portions. The extract was evaporated to dryness. The residue was dissolved in benzene (30 ml) and subjected to chromatography on an alumina column using 1:1 benzene–$CHCl_3$ as the eluent, collecting the first, light yellow zone. Evaporation of the eluate gave 0.32 g (21.5%) **1** as a light yellow powder; mp 148-151°C. IR spectrum (nujol), ν, cm^{-1}: 3460 (O–H), 3320 (N–H), 2223 (C≡N), 1718 (C=O), 1674 (C=N), 1600 (C=C), 1384, 1320 (C–Me), 1092 (C–C). Found, %: C 64.48; H 6.32; N 15.91. $C_{14}H_{15}N_3O_2$. Calculated, %: C 65.36; H 5.88; N 16.33.

4-(N-*D,L*-Leucyl)-8,11,15,18,22,25-hexa(pentyloxy)phthalocyanine (2). A sample of dinitrile **1** (0.2 g, 0.78 mmol) and 1,4-dipentoxyphthalonitrile **5** (1.17 g, 3.9 mmol) were added to a suspension of magnesium 1-pentylate obtained by dissolving magnesium (0.5 g) in 1-pentanol (20 ml) and heated at reflux with stirring for 6 h. The solvent was evaporated off and the solid residue was dissolved in acetic acid (50 ml). The solution obtained was diluted with water (100 ml). The precipitate formed was filtered off, washed with water until the wash water was neutral, dried at 120°C, and extracted with benzene. The extract was subjected to chromatography on an alumina column using 1:1 $CHCl_3$–benzene as the eluent, collecting the first bright green zone. The eluate was evaporated and the residue was recrystallized from 15 ml DMF to give 0.068 g (7.5%) **2** as green needles; mp 198-203°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: -0.41 (2H, s, NH); 0.68-1.22 (24H, m, CH_3); 1.43-2.44 (36H, m, CH_2); 3.12 (1H, s, CH); 3.39-3.71 (2H, m, NCH_2); 3.92-4.23 (4H, m, OCH_2); 4.61-4.82 (8H, m, OCH_2); 5.94 (1H, s, NH); 7.29-7.81 (6H, m, H_{arom}); 7.83-8.24 (4H, m, H_{arom}); 9.11 (1H, s, CO_2H). UV spectrum ($CHCl_3$), λ_{max}, nm (log ε): 790 (2.504), 763 (1.746), 731 (0.86), 461 nm (0.425); ($CHCl_3$+Py), λ_{max}, nm (log ε): 793 (1.234), 731 (1.164), 460 (0.423). Found, %: C 70.12; H 7.88; N 10.93. $C_{68}H_{89}N_9O_8$. Calculated, %: C 70.36; H 7.73; N 10.87.

Nickel Complex of Tetra-(N-*D,L*-leucyl)phthalocyanine (3). A thoroughly ground mixture of dinitrile **1** (0.2 g, 0.77 mmol) and nickel acetate dihydrate (0.06 g, 0.28 mmol) was maintained in a quartz test tube for 2 h at 190-200°C. The reaction mixture was then dissolved in conc. sulfuric acid (10 ml). The solution obtained was poured into water (100 ml). The precipitate formed was filtered off, washed consecutively with 3% ammonium hydroxide, 3% aq. acetic acid, and water until the wash water was neutral. Then, the precipitate was dried at 120°C. The dry precipitate was purified by extraction of impurities in a Soxhlet apparatus to give 0.11 g (55%) **3** as a blue powder, which does not melt up to 250°C. UV spectrum (DMF), λ_{max}, nm (log ε): 672 (1.21), 612 sh (0.21), 335 (0.43). Found, %: C 61.17; H 5.77; N 14.98. $C_{56}H_{60}N_{12}O_8Ni$. Calculated, %: C 61.83; H 5.56; N 15.45.

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