Bi(III) I-Complexes of Porphyrins for Biomedicine: Synthesis and Spectral-Optical Properties

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Abstract—Bismuth complexes of porphyrins are of interest for IR luminescence diagnostics of cancer, since rather intense emission bands in the range of 800–920 nm have been found. In connection with the COVID-19 pandemic, bismuth compounds are also of interest in the treatment of coronavirus infection. Bismuth complexes of porphyrins of various spatial configurations have been synthesized, and several spectral-optical properties have been investigated. The influence of various substituents on the spectral characteristics was evaluated by methods of studying electronic absorption spectra, luminescence spectra, IR-, and 1H NMR spectroscopy.

Keywords: bismuth complexes, porphyrins, spectral characteristics, IR luminescence, absorption spectra, coronavirus infection

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INTRODUCTION

Interest in bismuth preparations is primarily due to their use in medicine. The widespread use of bismuth in medical practice is explained by its very low toxicity in comparison, for example, with tin and lead, which have chemical properties similar to bismuth [1, 2]. In light of recent events, the use of bismuth compounds in the treatment of coronavirus infection is of interest.

Human coronavirus (Coronaviridae, Coronavirus) was isolated in 1965 by D. Tyrrell and M. Bynoe from patients with flu-like symptoms [3]. According to the modern taxonomic classification, all known human and animal coronaviruses are divided into four genera: α-, β-, γ-, and δ-coronavirus. A special place is occupied by the genus β-coronavirus, which includes dangerous causative agents of fatal pneumonia, SARS-CoV (severe acute respiratory syndrome coronavirus, better known as the SARS virus) and MERS-CoV (Middle East respiratory syndrome coronavirus). For the treatment of SARS-CoV, eight coordination complexes of bismuth were synthesized and then tested for inhibitory action against the helicase ATPase SARS-CoV and for duplex unwinding processes [4]. Previous studies [5–7] have demonstrated an extremely important role in the life cycle of the virus NTF/helicase protein, which made it a promising target in anti-SARS therapy. Apparently, bismuth ions can slow down the biocatalytic processes of SARS-CoV helicase due to the formation of an N-terminal metal-binding domain, a cysteine-rich region with which bismuth effectively binds to form Bi–S bonds. As shown by the data of the analysis of phosphate release, which measured the effectiveness of inhibition, as well as the results of the inhibitory action directed against duplex unwinding, the most effective of the synthesized compounds were precisely the bismuth complexes of porphyrins, Bi(NO3)-5,10,15,20-tetraphenylporphyrin and Bi(NO3)-5,10,15,20-tetrakis(4-methoxycarbonylphenyl)porphyrin.

It should be noted that so far no effective remedies have been found for the treatment of COVID-19, and it is possible that in the future bismuth porphyrin complexes (BiPCs) will find an application for the treatment of this ailment. BiPCs can also find application in IR luminescent diagnostics of cancer. Recently, it was shown that the most promising for biomedical diagnostic studies is the near-IR (NIR) spectral range due to the greater penetration depth of photons through biological tissue and insignificant autofluorescence in this spectral range (800–1100 nm) [8]. The fluorescence caused by the tissue itself is called autofluorescence. Depending on the wavelength, various fluorescent dyes are excited in biological tissues. Flavins have maximum excitation values in the ultraviolet and blue ranges of the spectrum. Maximum fluorescence occurs at 520 nm. Connective tissue (collagen and elastin) is also of great importance. The excitation band is 330–360 nm, and the fluorescence is in the
410-nm region. However, the main background chromophores are endogenous porphyrins, in which the absorption maximum is located in the region of 400 nm, and the fluorescence extends up to 750 nm, i.e., up to the beginning of the NIR spectral range. Thus, it can be concluded that the NIR spectral range has a minimal background autofluorescence.

The aim of this study was to synthesize and study the spectral-optical characteristics of BiPCs of various spatial configurations (Fig. 1). Etioporphyrin II (1), which has a flat structure, natural protoporphyrin IX (2), and various derivatives of tetraphenylporphyrin with COOCH3, isobutyl, mesityl group (3a, 3b and 3c, respectively), and the most spatially distorted, pentafluorophenylporphyrin (3d). The influence of these substituents on the spectral-luminescent characteristics was evaluated.

1. EXPERIMENTAL: EQUIPMENT, INSTRUMENTS, AND METHODS OF SYNTHESIS

Electronic absorption spectra (EAS) were recorded on a Helios Alpha Local Control System UV-vis spectrophotometer (TermoSpectronic, USA). The luminescence spectra were studied using an FSD-10 mini-spectrometer (Scientific and Technical Center Fiber Optic Devices LLC, Moscow). Spectra 1H NMR scale δ (ppm) were obtained on a Bruker DPX-300 instrument (300 MHz) (Germany) in deuterchloroform. Fourier transform infrared spectra were recorded on a Bruker EQUINOX 55 instrument (Germany) in the mid-infrared range (4000–700 cm⁻¹) as a powder in potassium bromide using the EasiDiff™ Diffuse Reflectance Accessory from PIKE Technologies Inc., and in the far IR range (700–50 cm⁻¹) in the form of a suspension in liquid paraffin on high density polyethylene windows. The spectra were processed using the OPUS 6.0 program.

The synthesis of etioporphyrin II (EP II) (1a) was carried out according to the Fisher method [9]. Dimethyl ester of protoporphyrin IX (PP IX DME) (2a) was obtained from blood hemin according to the method in [10]. 5,10,15,20-Tetrakis (4-methoxycarbonylphenyl) porphyrin [TPP(4-COOCH3Ph)] (3a) was synthesized from pyrrole and methyl ester of 4-formylbenzoic acid by the Rothemund method in propionic acid [11]. 5,10,15,20-Tetrakis-mesitylporphyrin (TPP) (4a), tetrakis(4-isobutyl)phenylporphyrin [TPP(4-iBuPh)] (4c), and pentafluorophenylporphyrin (TPPF20) (5a) were obtained by the Lindsey method [12]. Synthesis of bismuth complexes EP II, PP IX DME, TPP(4-COOCH3Ph), TMP, and TPPF20 was described in [13].
2. RESULTS

2.1. Electronic Absorption Spectra

EAS of bismuth complexes (Table 1) show a significant bathochromic shift of the Soret band (up to 477 nm) compared to the free bases of porphyrins and the fusion of 4 Q-bands of the free base of porphyrins characteristic of complexation to 2 Q-bands (or 1st band in the case of Bi(III)I-PP IX DME and Bi(III)I-TPPF$_{20}$) due to the redistribution of the electron density (Fig. 2).

In contrast to metal-free porphyrins, BiPCs have a deep green color.

2.2. IR Spectroscopy

Comparison of the IR absorption spectra of the initial porphyrins considered in this study shows that no significant differences in the vibrations of the nitrogen–carbon cycles are observed. Table 2 shows the frequencies of deformation vibrations. Nevertheless, there is a natural increase in the number of bands in this region, associated with the complication of the structure of the molecule and an increase in the number of different CCC fragments, the inclusion of aromatic rings in the molecule. We can only note a slight increase in the frequencies of deformation vibrations of the $\delta$(CNC) cycle on going to the tetraphenylporphyrin spectrum. The picture naturally changes on going to bismuth complexes (Fig. 3). In the long-wavelength regions of the spectra, bands of bond vibrations are observed $\nu$(Bi–I) with frequencies of 90–130 cm$^{-1}$, the motions of these heavy atoms disturb the additional deformation vibrations of the nitrogen–carbon ring. The bands of bending vibrations with the participation of bismuth, iodine, and nitrogen atoms, $\delta$(NBiI), with frequencies of 150–165 cm$^{-1}$ lie somewhat higher. The frequencies of bending vibrations of the pyramid [BiN$_4$] are even higher. And finally, in the area of 335–375 cm$^{-1}$, the frequencies of stretching vibrations of this fragment of the complex with the participation of deformations of the nitrogen–carbon ring.

| Compound                  | $\lambda_{\text{max}}$ nm (log$\varepsilon$) |
|---------------------------|---------------------------------------------|
|                           | Soret Strip                                 |
|                           | Q-bands                                     |
| Bi(III)I-EP II            | 474                                         | 532, 575                                  |
| Bi(III)I-PP IX DME        | 477 (4.85)                                  | 586 (4.07)                                |
| Bi(III)I-TPP(4-COOCH$_3$Ph) | 472 (5.03)                                | 600 (3.87), 646 (3.96)                     |
| Bi(III)I-TMP              | 474 (5.17)                                  | 605 (3.91), 653 (4.01)                     |
| Bi(III)I-TPP (4-iBuPh)    | 474                                         | 600, 653                                  |
| Bi(III)I-TPPF$_{20}$      | 473 (5.18)                                  | 589 (4.13)                                |

Fig. 2. Electronic absorption spectra Bi(III)I-complex PP IX DME (1) and Bi(III)I-complex EP II (2).

Fig. 3. IR absorption spectra of (1) TMP and (2) Bi(III)I-TMP complex in the range of vibrational frequencies of the porphyrin ring.
2.3. Luminescence Spectra

Spectra luminescence BiPCs (Fig. 4) showed the presence of two emission bands: 650–800 nm (with a maximum in the vicinity of 730 nm) and 800–920 nm (with a maximum in the 900-nm region). Note that the first band is the main and most intense one. As was established in [14], upon passing from the crystalline form of Bi-complexes to their solutions, one broad emission band is transformed into a two-band structure. In this case, the transition from the aggregated state of the complex to the non-aggregated state is carried out.

Thus, the presence of an emission band in the BiPCs in the NIR spectral range was confirmed, which shows the possibility of using these complexes for the purposes of luminescent diagnostics of neoplasms. In this connection, it is advisable to carry out further studies of the photophysical properties of a number of BiPCs (in particular, the luminescence lifetime, quantum yield, etc.).

CONCLUSIONS

(1) Comparative studies of the EAS of bismuth complexes of porphyrins show a significant bathochromic shift of the Soret band (up to 477 nm) compared to the free bases of porphyrins.

Table 2. The vibration frequencies of the IR spectra of the BiPC in the region of porphyrin ring vibrations (cm\(^{-1}\))

| Bi(III)I-PP IX | Bi(III)I-TMP | Bi(III)I-TPPF\(_{20}\) | Bi(III)I-TPP(4-COOMePh) | Bi(III)I-EP II |
|---------------|-------------|-----------------------|--------------------------|---------------|
| v, cm\(^{-1}\) | v, cm\(^{-1}\) | v, cm\(^{-1}\) | v, cm\(^{-1}\) | v, cm\(^{-1}\) |
| 110 | 117 | 91 | 80 | 101 | \(\nu\) (BiI) + \(\nu\)\(_{\text{as}}\) (BiN) |
| 132 | 134 | 122 | 120 | 125 | \(\delta\) (BiNC) + \(\nu\) (BiN) + \(\nu\) (BiI) |
| 165 | 161 | - | - | 156 | \(\nu\) (BiI) + \(\nu\) (BiN) + \(\delta\) (BiNC) |
| 182 | 176 | 175 | 173 | \(\nu\) (BiN) + \(\delta\) (BiNC) + \(\delta\) (BiI) |
| 226 | 217 | 202 | 204 | 228 | \(\delta\) (BiNC) + \(\delta\) (BiI) |
| 248 | 236 | 212 | 242 | \(\delta\) (BiNC) |
| 226 | 260 | 267 | 253 | 277 | \(\delta\) (BiNC) |
| 248 | 290 | 280 | 280 | 301 | \(\delta\) (NBiN) + \(\delta\) rings |
| 300 | 314 | - | 293 | | |
| 348 | 336 | 340 | 346 | 346 | \(\nu\) (BiN) + \(\delta\) (BiNC) |
| 362 | 375 | 368 | 372 | 373 | |
| 427 | 419 | 397 | 396 | 399 | \(\delta\) (CNC) + \(\delta\) rings + \(\delta\) (NBiN) |
| 500 | 470 | 471 | 490 | 467 | \(\delta\) (CNC) + \(\delta\) rings + \(\delta\) (NBiN) |
| 504 | 504 | | | 461 | |
| 523 | 523 | | | 492 | |
| 568 | 569 | 566 | 572 | 561 | \(\delta\) (CNC) + \(\delta\) rings |
| 582 | 582 | | | | |
| 643 | 640 | 646 | 637 | 624 | \(\delta\) (CNC) + \(\delta\) rings |
| 667 | 667 | 670 | 650 | | |
| 687 | 690 | 682 | 684 | 662 | |
| | | | | 679 | |
(2) In the IR spectra, when the bismuth ion is coordinated with porphyrin macrocycles, vibration bands with the participation of bismuth or iodine and bismuth-nitrogen bonds appear in the long-wavelength regions of the spectra.

(3) The study of the luminescence spectra showed that Bi-complexes in various organic solutions have a two-band structure, with the main and most intense band in the range of 650–800 nm. The second emission band observed in BiPCs (800–920 nm) makes it possible to use these complexes for the purposes of luminescent diagnostics of cancer.

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