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Synthesis, spectral, structural and antimicrobial studies of fluorinated porphyrins

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ABSTRACT

We have reported the synthesis, spectral and anti-microbial studies of 5,10,15,20-tetrakis(4′-trifluoromethylphenyl)porphyrin derivatives, MT(4′-CF_3P)Ps where M = 2H, **1**; Fe(II), **2**; Ni(II), **3**; Cu(II), **4**; Zn(II), **5** and Pt(II), **6**. The optical absorption and steady state fluorescence spectra of **1**–**6** show characteristic bands comparable with MTPPs. Compounds **1** and **3**–**5** were structurally characterized using single crystal X-ray diffraction analysis; **1** and **4** crystallized in the triclinic system, whereas **3** and **5** in the monoclinic system. The high spin nickel(II) ion in **3** is well placed at the center of the planar porphyrin core, which is influenced by the presence of trifluoromethylphenyl groups at the periphery and two THF molecules in apex positions. The porphyrins **1** and **3**–**5** are arranged in a slip-stacked fashion involving C–H···π and C–F···$H_{(sol)}$ intermolecular close contacts for **1**, **4** and **3**, **5**, respectively. The role of non-covalent interactions involving the trifluoromethylphenyl groups in the crystal packing have been analyzed and quantified using Hirshfeld surface analysis. The antimicrobial activity of the free ligand is higher compared to its metal complexes.

1. Introduction

Porphyrinoids have been widely studied due to their spectroscopic, electrochemical luminescent properties and their novel biological activities. Synthetic porphyrin analogues closely resemble naturally occurring tetrapyrrole macrocycles and hence they are considered to be the appropriate ligands of choice for mimicking the natural processes [1]. The introduction of suitable substituents at the peripheral positions of the porphyrin core provokes tunable shape, size and symmetry and are found in material [2] and therapeutic applications [3,4]. It is well known that the pharmacological properties of organic molecules can be enhanced by the incorporation of fluorine atoms which subsequently makes them more abundant in the market as effective drugs. In particular, drugs containing trifluoromethylphenyl groups, such as Prozac, Sensipar, Arava, Travatan, etc., are innumerable which leads to the huge success of fluorine containing drugs in medicinal chemistry [5,6]. It is essential to analyze the various intermolecular interactions which control the structure–property relationship of the fluorinated drugs in binding to enzyme active sites. Moreover, upon fluorination, the pharmaco-kinetic properties of the molecules are pronounced which leads to better binding and hence the superior biological activity [7].

Porphyrin derivatives are excellent materials in crystal engineering [8–10] and we are interested in the design and engineering of fluorinated porphyrins in order to understand the role of close contacts involving fluorine in the crystal packing. Although fluorine substituted porphyrins and their analogues have been actively studied in the recent years [11–13], it is noted that detailed investigations on the structure and photophysical properties of fluorinated porphyrins are limited. In this line, we were stimulated to investigate the spectral and quantitative crystal structure analysis of electron deficient fluorinated metalloporphyrins containing trifluoromethylphenyl groups (Fig. 1) and the influence of such groups in the crystal packing motif of the porphyrins using Hirshfeld surface analysis [14]. Also, the antimicrobial properties of the free ligand and their metal complexes were examined with two Gram-negative and two Gram-positive bacterial strains, and one fungal strain.

2. Experimental

2.1. Materials and methods

The chemicals employed for the synthesis and used in other processes were commercially available reagents of analytical grade

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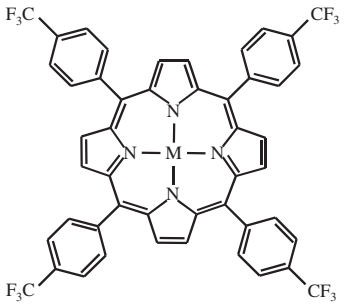

M = 2H, **1**; Fe(II), **2**; Ni(II), **3**; Cu(II), **4**; Zn(II), **5** and Pt(II), **6**

Fig. 1. Molecular structure of the porphyrins under study.

and were used without further purification unless otherwise specified. The solvents used for the synthesis were purified using the available literature methods [15]. Optical spectra were recorded at room temperature in CH_2Cl_2 using a Systronics double beam 2202 spectrophotometer and ^1H NMR spectra were taken in a Bruker Avance III 400 MHz spectrometer. Mass spectra were recorded under ESI/HR-MS at 61 800 resolution using a Thermo Scientific Exactive mass spectrometer (Thermo Fischer Scientific, Bremen, Germany). Fluorescence spectra and quantum yield measurements were performed using a Perkin Elmer LS 55 luminescence spectrophotometer.

2.2. Synthesis of 5,10,15,20-tetrakis-(4′-trifluoromethylphenyl)porphyrin, $H_2T(4'\text{-}CF_3P)P$ and the metal complexes $MT(4'\text{-}CF_3P)P$; M = Fe(II), Ni(II), Cu(II), Zn(II) and Pt(II)

Pyrrole (0.5 mL, 7.2 mmol) and 4-(trifluoromethyl) benzaldehyde (1.0 mL, 7.2 mmol) were taken in a 500 mL two necked round bottom flask containing 350 mL of CH_2Cl_2 and the content was purged with N_2 gas for 15 min. Then, the acid catalyst $BF_3{\cdot}OEt_2$ (0.1 mL, 2.5 M) was introduced and the solution was stirred at room temperature for 1 h under an inert atmosphere, followed by the addition of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DDQ (760 mg). The reaction mixture was further stirred for one more hour at room temperature in air, the solvent was removed by a rotary evaporator, then purified by column chromatography using silica and hexane/chloroform as the eluent afforded the free ligand **1** in 35% yield (550 mg). The zinc(II) and copper(II) complexes were synthesized in a chloroform/methanol mixture using the corresponding metal acetate, and the yields were obtained as 92% and 94%, respectively. The nickel(II) and iron(II) complexes were prepared in DMF using the metal chloride as the metal ion carrier, and the yield was found to be 61% and 74%, respectively. The platinum(II) complex [16] was prepared in benzonitrile using $K_2[PtCl_6]$ as the metal ion carrier and the yield was found to be 85%. UV–Vis data of porphyrins in CH_2Cl_2, λ_{max} (log $\varepsilon/M^{-1}\,cm^{-1}$): **1**, 417 (5.81), 512 (4.59), 552 (4.21), 588 (4.20), 645 (3.99); **2**, 415 (5.86), 508 (4.87), 573 (4.33); **3**, 413 (6.26), 526 (5.31); **4**, 413 (6.10), 537 (4.86); **5**, 418 (6.28), 548 (5.03); **6**, 399 (6.20), 508 (5.17), 541 (4.67). ^1H NMR data for **1** in $CDCl_3$ (400 MHz): 8.81 (s, 8H, -pyrrole-H), 8.33–8.35 (d, 8H, J = 8.00 Hz, *o*-phenyl-H), 8.04–8.06 (d, 8H, J = 8.00 Hz, *m*-phenyl-H), −2.84 (br, 2H, imino-H). ^1H NMR data for **3** in $CDCl_3$ (500 MHz): 8.91 (s, 8H, -pyrrole-H), 8.34–8.36 (d, 8H, J = 8.00 Hz, *o*-phenyl-H) 8.04–8.06 (d, 8H, J = 8.00 Hz, *m*-phenyl-H). ^1H NMR data for **5** in $CDCl_3$ (500 MHz): 8.92 (s, 8H, -pyrrole-H), 8.34–8.36 (d, 8H, J = 8.00 Hz, *o*-phenyl-H), 8.04–8.06 (d, 8H, J = 8.00 Hz, *m*-phenyl-H). ESI-mass data of **1**: 887.20 (calcd: 886.73).

2.3. X-ray crystal structure analysis

Suitable single crystals of the porphyrin ligand and its metal complexes were mounted on a glass capillary and the data collections were performed on a Bruker AXS Kappa Apex II CCD diffractometer with graphite monochromated Mo Kα radiation (λ = 0.71073 Å) at 298 K. The reflections with $I > 2\sigma(I)$ were employed for the structure solution and refinement. The SIR92 [17] (WINGX32) program was used for solving the structure by direct methods. Successive Fourier synthesis was employed to complete the structures after full-matrix least squares refinement on $|F|^2$ using the SHELXL97 [18] software.

2.4. Hirshfeld surface analysis

Hirshfeld surface analysis and the generation of 2D fingerprint plots were performed using *Crystal Explorer 3.1* [14].

2.5. Antimicrobial studies

The antimicrobial activity of the free ligand and its metal complexes were performed using the literature method [19] against MTCC cultures, which were obtained from the Microbial culture collection, Chandigarh, India and are as follows: two Gram-positive, *Staphylococcus aureus*, *Bacillus subtilis* and two Gram-negative *Pseudomonas aeruginosa*, *Escherichia coli* bacterial strains, and the fungal strain *Candida albicans*. The ligand and its metal complexes were dissolved in dimethylsulfoxide (DMSO) to a stock solution of 250 μg/mL. The sample was loaded onto sterile discs on agar plates directly. Plates swabbed with the bacteria culture were incubated at 35–37 °C for 24 h. At the end of the incubation period, the inhibition zones formed on the medium were evaluated in mm and studies were performed in duplicate. A solvent control test was also performed in order to study the effect of dimethylsulfoxide on the growth of the microorganisms, but it showed no activity against the microbial strains. A standard antimicrobial drug (tetracycline) was also screened under similar conditions for comparison.

3. Results and discussion

3.1. Synthesis of the porphyrin ligand and its metal complexes

The synthesis of 5,10,15,20-tetrakis-(4′-trifluoromethylphenyl)-porphyrin $H_2T(4'\text{-}CF_3P)P$, **1**, has been carried out using a modified procedure of Lindsey et al. [20] and its metal complexes $MT(4'\text{-}CF_3P)P$ (M = Fe(II), **2**; Ni(II), **3**; Cu(II), **4**; Zn(II), **5** and Pt(II), **6**) were prepared by a variant literature methods [16,21,22]. The synthesized porphyrins were isolated, purified by column chromatography and characterized by UV–Vis and ^1H NMR spectroscopic methods, mass spectrometry and single crystal X-ray diffraction analysis.

*3.2. Photophysical properties of the porphyrins, **1**–**6***

The electronic absorption spectra of the porphyrin ligand and its metal complexes exhibited an intense Soret (B) and four/two/one visible (Q) bands, and these absorption spectral features are similar to those of the corresponding MTPPs [23]. The intensity of the Soret band is high due to an allowed $^1A_{1g} \rightarrow {}^1E_u$ transition and the peak position is in the range 413–418 nm in dichloromethane as the solvent (except for **6**, 399 nm). The overlayed UV–Vis spectra of **1**–**6** are shown in Fig. S1 and it is observed that there is a marginal red shifted absorption spectrum for the zinc(II) complex and a marginal blue shifted absorption spectra