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Synthesis, Spectroscopic Properties and Biological Studies of Mixed Ligand Zirconium (IV) Porphyrinates

KEYWORDS: porphyrin, zirconium, salicylate, antibacterial study

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ABSTRACT *The synthesis of new zirconium mixed ligand porphyrin complexes 5-XSAZrTTP, where 5-XSA(X= -Cl, -F, -NO2, -CH3, -NH2)= substituted salicylate – the out planed ligand, and TTP – the dianion of 5,10,15,20-tetra-p-tolyl-21H,23H-porphineis reported. The obtained complexes are characterized by UV–Vis, 1H NMR, IR, and ESI Mass spectroscopy. Beside fluorescence, the complexes were also screened for biological studies.*

1. Introduction

Porphyrinderivatives have been applied in different fields of science and technology – from electronic and catalysis to medicine[1-4]. A variety of biological activities exhibited by porphyrins is due to the fact that natural and synthetic porphyrins have relatively low toxicity in vitro and in vivo and they possess antitumor and antioxidant effects and have a good potential for metal ions complexation. Introduction of the substituents on the periphery of the porphyrin macrocycle and/or directly to the central metal atom can change both electronic and physicochemical properties of the porphyrin system as a whole[5]. The present work is dedicated to the synthesis, spectroscopic characterization and biological study of novel mixed-ligand complexes of zirconium (IV) porphyrin with substituted salicylate as out-planed ligands.We believe that these novel compounds will be fundamental substances for potential applications in the future.

2. Experimental

All the chemicals were of analytical grade and used as received unless otherwise noted. Pyrrole was distilled over potassium hydroxide pellets under vacuum prior to use. All the organic solvents that were used for the synthesis and for chromatographic separations were dried before use. Elementary analysis (C, H, N and S) were obtained on a Vario EL III and CHNS-932 Leco Elemental Analyzer. UV-Vis spectra, Infrared spectra, ^{1}H NMR spectra were recorded on a T90+ UV/VIS spectrophotometer, Perkin Elmer-spectrum 400 FTIR spectrophotometer(KBr pellets), and BrukerAvance II 500 (500 MHz)(using tetramethylsilane as internal standard and $CDCl_3$ as solvent) respectively. Fluorescence measurements were performed on Synergy MX BIOTEK Multimode Reader.

Antibacterial studies

The antibacterial activity was evaluatedby agar-well diffusion method[6] with modifications. The 0.1 µM of test compounds in dimethyl sulphoxide were tested against three Gram positive bacteria (Bacillus subtilis,Staphylococcus aureus,and Enterococcus faecalis) and three Gram negative bacteria (Klebsiella pneumonia,A lcaligenesdenitrificans, and Micrococcus luteus). 20 mL of sterilized nutrient agar was inoculated with 100 µL of bacterial suspension (10^8 CFU/mL) and then, poured on to sterilized petri plate. The agar plate was left to solidify at room temperature. A well of 4mm was aseptically bored into the agar plate. Then, 20 µL of the complexes was added in each well. The plates were kept at 4°C for 2 hours to allow the dispersal and then incubated at 37 °C for 24 hour.

1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging assay

In this assay, free radical scavenging activity was determined by measuring the bleaching of purple-colored methanol solution of DPPH radical. The radical scavenging activity was determined according to the method of Blois et al.with modifications. A total of 1 ml from a 0.5 mM methanol solution of the DPPH radical was mixed to 2 ml sample and to this 2 ml of 0.1 M sodium acetate buffer(pH 5.5) was added. The mixtures were well shaken and kept at room temperature in the dark for 30 min. The absorbance was measured at 517 nm using a double beam UV-VIS spectrophotometer.The radical scavenging activity (RSA) was calculated as a percentage of DPPH radical discoloration, using the equation: $\%RSA = [(A_0 - A_s)/A_0] \times 100$where, A_0 is the absorbance of the control and A_s is the absorbance of the test compound.

2.1. Synthesis of axially ligated zirconium(IV) porphyrins complexes(Scheme I).

Synthesis of H2TTP.The free base 5,10,15,20-tetra-p-tolylporphyrin(H_2TTP) was synthesized by the direct condensation of pyrrole with substituted benzaldehydes[7].

Synthesis of dichloro(5,10,15,20-tetra-p-tolylporphyrinato) zirconium(IV), Cl2Zr(TTP).TheCl_2Zr(TTP) was obtained by the reaction of H_2TTP with zirconium(IV)chloride by benzonitrile method[8].

Cl2Zr(TTP).Red solid; Anal.Calcd.:C, 69.38; H, 4.37; N, 6.74; Found: C, 69.53; H, 4.56; N, 6.68; UV-vis(λ_{max}, nm) $CHCl_3$: 414, 542; ESI-MS(CH_3OH): m/z calcd. 830.96; found 831.04 ($[M+H]^+$). IR(KBr, ν, cm^{-1}): 492(ν_{Zr-N}); ^{1}HNMR($CDCl_3$, δ):8.80(8H, s, pyrrole), 8.28(4H, s, o-phenyl), 8.00(4H, s, o-phenyl), 7.65(8H, s, m-phenyl), 2.70(12H, s, p-CH_3).

Synthesis of axially ligated Zr(IV) porphyrins: 5-XSAZr(TTP):

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Cl_2Zr(TTP) (0.15mmol) in 25 ml $CHCl_3$and respective salicylate (0.56mmol) in 25ml CH_3OH was stirred under reflux for 12 hour[9]. After concentration, extracted with distilled water, filtered through anhydrous $Na_2SO_4$and was recrystallized from dichloromethane-hexane solution (1:1). The same procedure was applied for the synthesis of all axially ligated zirconium porphyrin complexes as described above. The purified axially ligated zirconium porphyrin complexes were obtained in yields of 40-45%.

5-ClSAZr(TTP).Red solid; Anal.Calcd.:C, 70.99; H, 4.22; N, 6.02; Found: C 70.64, H 4.53, N 6.23; UV-vis(λ_{max}, nm) $CHCl_3$: 421, 552, 595; ESI-MS(CH_3OH): m/z calcd. 930.60; found 931.04([M+H]$^+$). IR(KBr, ν,cm^{-1}): 485($\nu_{Zr\text{-}N}$), 668($\nu_{Zr\text{-}O}$), 721($\nu_{Zr\text{-}O}$); ^{1}HNMR(CDCl3,δ):8.96(8H, s, pyrrole), 8.53(4H, s, o-phenyl), 8.11(4H, s, o-phenyl), 7.71(8H, s, m-phenyl), 2.73(12H, s, p-CH_3), 7.10-7.29(1H, q, H-4), 7.15 -7.16(1H, d, H-3), 7.19(1H, s, H-6).

5-FSAZr(TTP).Brown solid; Anal.Calcd.:C, 72.26; H, 4.30; N, 6.13; Found: C72.55, H 4.23, N 6.10; UV-vis(λ_{max}, nm) $CHCl_3$: 423, 551, 597; ESI-MS(CH_3OH): m/z calcd. 914.15; found 915.34 ([M+H]$^+$). IR(KBr, ν_{max}, cm^{-1}): 492($\nu_{Zr\text{-}N}$), 660($\nu_{Zr\text{-}O}$), 722($\nu_{Zr\text{-}O}$); ^{1}HNMR($CDCl_3$, δ): 9.26(8H, s, pyrrole), 8.46(4H, s, o-phenyl), 8.23(4H, s, o-phenyl), 8.08(8H, s, m-phenyl), 2.71(s,12H, p-CH_3), 7.10-7.30(1H, q, H-4), 7.15-7.17(1H, d, H-3), 7.19(1H, s, H-6).

5-NO2SAZr(TTP). Red solid; Anal.Calcd.:C, 70.19; H, 4.18; N, 7.44; Found: C 70.89, H 4.38, N 7.15; UV-vis(λ_{max},nm) $CHCl_3$: 425,555, 594; ESI-MS(CH_3OH): m/z calcd. 941.15; found 942.01([M+H]$^+$). IR(KBr, ν_{max}, cm^{-1}): 487($\nu_{Zr\text{-}N}$), 667($\nu_{Zr\text{-}O}$), 728($\nu_{Zr\text{-}O}$); ^{1}HNMR($CDCl_3$, δ): 9.10(8H, s, pyrrole), 8.47(4H, s, o-phenyl), 8.18(4H, d, o-phenyl), 7.78(8H, s, m-phenyl), 2.85(s,12H, p-CH_3), 7.06-7.19 (1H, q,H-4),7.08-7.10 (1H, d, H-3), 7.17 (1H, s, H-6).

5-NH2SAZr(TTP). Reddish brownsolid; Anal. Cal.:C, 72.50; H, 4.54; N, 7.69; Found: C 72.53, H 4.34, N 7.76; UV-vis(λ_{max},nm)$CHCl_3$: 421, 549, 587; ESI-MS(CH_3OH:CH_3CN): m/z calcd. 911.17; found 911.23([M+H]$^+$); IR(KBr, ν, cm^{-1}): 500($\nu_{Zr\text{-}N}$), 678($\nu_{Zr\text{-}O}$), 722($\nu_{Zr\text{-}O}$,); ^{1}H NMR($CDCl_3$,δ): 9.06(8H, s, pyrrole), 8.52(4H, s, o-phenyl), 8.13(4H, d, o-phenyl), 7.71(8H, s, m-phenyl,), 2.87 (12H, s, p-CH_3), 7.09-7.24(1H, q, H-4), 7.15-7.18(1H, d, H-3), 7.20(1H, s, 6-H).

5-CH3SAZr(TTP).Red solid; Anal.Calcd.: C, 73.90; H, 4.65; N, 6.16; Found: C 73.14, H 4.21, N 6.05; UV-vis (λ_{max}, nm) $CHCl_3$:422, 553, 595; ESI-MS(CH_3OH:CH_3CN): m/z calcd 908.23; found 909.44([M+H]$^+$); IR(KBr, ν cm^{-1}): 517($\nu_{Zr\text{-}N}$), 685($\nu_{Zr\text{-}O}$), 715($\nu_{Zr\text{-}O}$); ^{1}HNMR($CDCl_3$, δ): 8.90(8H, s, pyrrole), 8.50(4H, s, o-phenyl), 8.18(4H, s, o-phenyl), 7.68(8H, m, m-phenyl), 2.85(12H, s, p-CH_3), 7.06-7.12(1H, q, H-4), 7.18-7.19(1H, d, H-3), 6.89(1H, s, H-6).

3. Results and Discussion

Spectral Analysis of Cl2Zr(TTP) and 5-XSAZr(TTP): The 5,10,15,20-tetrakis(4-methylphenyl)porphyrin(H2TPP) spectrum contains a typical B band at 420 nm and shows four less-intensive Q bands. The number and intensity of UV-Vis bands of zirconium porphyrinwasdecreased when compare with H_2TTP(Figure 1). This may be due to the increasing in symmetry of monomer structure and the energy gap decreased as compared to H_2TTP[10].In axially ligated zirconium(IV) porphyrin complexes both B and Q band regions of the spectra show slight red shift. The red shift may be due to structural distortion in the porphyrin macrocycle, and concomitant electronic coupling of the metalloporphyrin to the salicylate mediated by the zirconium metal ion[11]. The appearance of characteristic ν(Zr-N) vibration frequency at ~500-430cm^{-1}indicated the formation of zirconium(IV) porphyrin compounds[12]. The incorporation of salicylates in Zr(IV) metal derivatives i.e., 5-XSAZr(TTP), is confirmed by the appearance of Zr–O vibrational frequencies in the range 690–662cm^{-1} and 740–719cm^{-1} corresponding to the ligation of zirconium to oxygen of phenolic and carboxylic groups of salicylate respectively[13,14].In all the metallatedporphyrins, the absence of N-H protons of porphyrin and down-field shift in porphyrin protonindicated the insertion of zirconium in porphyrin macrocycle[15].In 5-XSAZrTTP complexes, the signals of axial salicylate protons were found to be up field shifted in comparison to the signals of porphyrin protons as well as in comparison to proton signals of free salicylic acid derivatives. These positions of protons show that axial ligand is under the influence of π-conjugated system of porphyrin macrocycle. The monomer complex formation of salicylate ligated zirconium(IV) porphyrins were characterized by the presence of the molecular ion peak in mass spectra.

The Cl_2Zr(TTP) and 5-XSAZr(TTP)complexes are emissive and show intraligand fluorescence comparable to other regular metalloporphyrins(Table 1).However, the emission bands of Zr(IV)porphyrins are blue shifted compared to free base porphyrins. This behavior is attributed to an enhanced spin–orbit coupling induced by the presence of the heavy-atom central metals in zirconium(IV)porphyrins complexes,which leads to a more efficient intersystem crossing from the lowest porphyrin singlet excited state $^1S_1(\pi, \pi^*)$ to the corresponding triplet manifold and thus reduces the probability of fluorescent emission[16].

A summary of the biological activity results is shown in Table 2.Our results demonstrated antibacterial activity against most of the zirconium(IV)porphyrin complexes and by comparing these complexes with H_2TTPwe noted that introducing zirconium and axial ligand in H_2TTP increased antibacterial activity. The results of the antioxidant studies(Table 2) showed promising results and 5-NO_2SAZr(TTP) showed remarkable radical scavenging activity with the lowest IC_{50} value.

4. Conclusion:

This paper presents the results of investigation of different salicylate ligated zirconium(IV)porphyrin complexes by various spectroscopic methods. The octahedral geometry is proposed on the basis of these spectral techniques.The antibacterial and radical scavenging activity of Zirconium(IV)porphyrin derivatives of salicylic acidis higher as compared to ligand.

Table 1.The fluorescence band maxima data of some selected complexes.

Compound	λmax,nm	
	Q(0,0)	Q(0,1)
H_2TTP	653	715
Cl_2Zr(TTP)	-	653
5-FSAZr(TTP)	608	657
5-NO_2SAZr(TTP)	606	654
5-NH_2SAZr(TTP)	611	660

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Table 2: Antibacterial assay by agar well diffusion assay and 1,1-Diphenyl-2-picrylhydrazyl (DPPH) radical scavenging assay

PORPHYRIN	Zone of inhibition(mm)						DPPH radical scavenging activity (IC_{50} µg/ml)
	K. pneumoniae	E. faecalis	A. denitrificans	M. luteus	B. subtilis	S. aureus	
H_2TTP	-	1	-	-	-		-
$Cl_2Zr(TTP)$	-	1.25	-	1	-	-	-
5-ClSAZr(TTP)	1.15	-	1.25	-	-	-	102
5-FSAZr(TTP)	2	_	-	-	1.5	1.5	44
5-NO_2SAZr(TTP)	2	1.4	1	1.5	2	1.5	37.5
5-NH_2SAZr(TTP)	1	-	1.25	1.5	-	1	87
5-CH_3Zr(TTP)	-	1.5	-	-	1	-	-
Control Chloramphenicol	2.5	1.4	2	2.25	2	2.1	

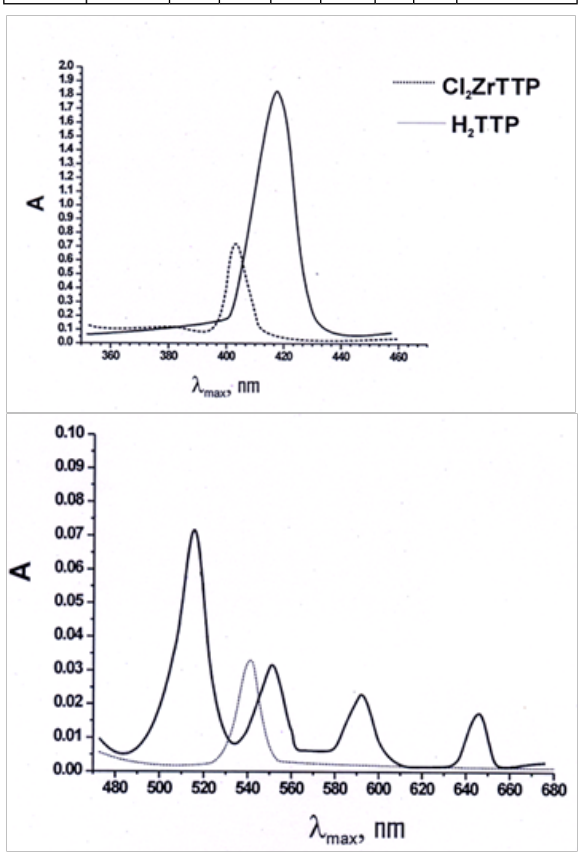
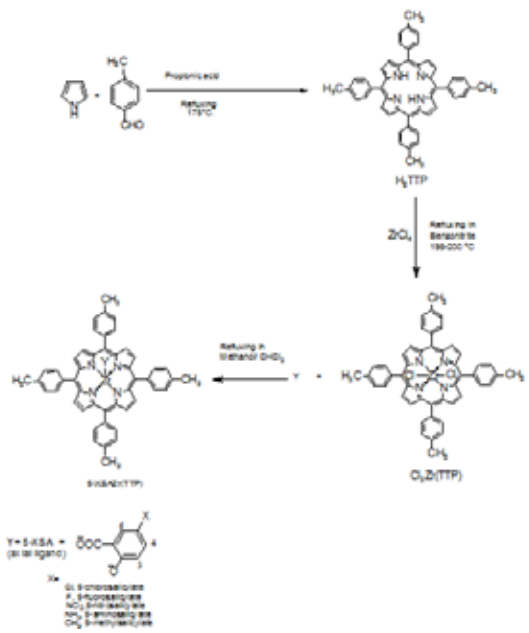


Figure 1: UV-vis overlapped (a) B bands (b) Q bands of H_2TTP and $(Cl)_2Zr(TTP)$.



Scheme 1: General scheme for preparation of zirconium porphyrin complexes

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