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Crystal structure and spectral properties of vitamin K3 based nitrobenzo[*a*]phenoxazines

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ABSTRACT

Benzo[*a*]phenoxazines are the planar polycyclic fluorescent compounds, find a variety of applications in biological sciences and are of growing interest. In the present work we synthesized heterocyclic aromatic fluorescent benzo[*a*]phenoxazines namely, 6-methyl-9-nitro-5H-benzo[*a*]phenoxazin-5-one (**1**) and 6-methyl-10-nitro-5H-benzo[*a*]phenoxazin-5-one (**2**) which are characterized in terms of the ^{1}H and ^{13}C chemical shifts from 2D gHSQCAD NMR experiments. Single crystal X-ray experiments revealed both **1** and **2** possess the C–H···O interactions. Moreover the π···π stacking interactions between planar polycycles have been noticed only in **1**. The structural and vibrational spectral inferences obtained from experiments are corroborated through the ωB97xD based density functional theory.

1. Introduction

Phenoxazine and benzo[*a*]phenoxazine derivatives represent oxygen or nitrogen containing heterocycles having three to five rings which are fluorescent and owing to their high molar absorption coefficient, better photo- [1] and thermostability, thermochromic [2] as well as solvochromic behaviour [3] find applications as metal- [4], pH- [5], gas (H_2S)- sensor [6]. The non-toxicity in comparison with other dyes [1] makes them interesting. Moreover the benzo[*a*]phenoxazine or benzo[*a*]phenoxazinium salts exhibiting strong fluorescence in the red region of the electromagnetic spectrum (> 600 nm) facilitates their use as long wavelength fluorophores [7,8] and preferred for the biological application [9–14]. The most widely known fluorescent benzo[*a*]phenoxazine derivatives are Meldola's blue, Nile red, Nile blue [15]. Benzo[*a*]phenoxazine moieties which serve as fluorescent probes [16–19] or as photosensitizers in (PDT) photodynamic therapy [20,21]. Besides some of benzo[*a*]phenoxazine derivatives also possess biological activities and widely been used in anti-tuberculosis [22], anti-inflammatory [23] antimalarial [24], anti-proliferative [25–27], antitumor [28], antibacterial [29], multidrug resistance activities [30] and to prevent human amyloid disorders [31].

The synthesis and characterization of benzo[*a*]phenoxazine derivatives from vitamin K3 [32] was carried out earlier in our laboratory. The antiproliferative activity against human breast adenocarcinoma cell line (MCF-7), human carcinoma (HeLa) cell line and normal skin cell line [32] of such derivatives in particular their selectivity toward toxic to malignant cells and not to normal cells [26] motivated us to extend this work with the synthesis and characterization of nitro derivatives of benzo[*a*]phenoxazine referred hereafter in this report as **1** (6-methyl-9-nitro-5H-benzo[*a*]phenoxazin-5-one) and **2** (6-methyl-10-nitro-5H-benzo[*a*]phenoxazin-5-one).

2. Experimental

2.1. General materials and methods

Vitamin K3 (2-methyl-1,4-naphthoquinone), 2-amino-4-nitrophenol and 2-amino-5-nitrophenol obtained from Sigma-Aldrich; toluene, methanol and silica-gel with 60–120 mesh size used for column chromatography were procured directly from Merck Chemicals, India. Solvents were distilled using standard procedures [33] and dried wherever necessary.

FT-IR spectra were recorded in 4000–400 cm^{-1} as KBr pellets on

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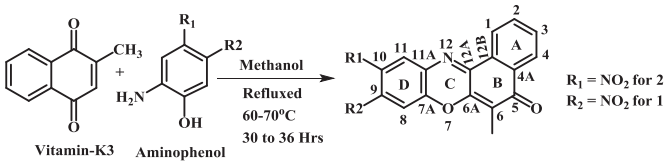

Scheme 1. Synthesis of benzo[*a*]phenoxazine from vitamin K3.

SHIMADZU FT 8400 spectrometer which are shown in Fig. S1 to Fig. S3 of ESI†. UV–Visible spectra of compounds on SHIMADZU UV 1650 in DMSO solvent in the range 200–800 nm (displayed in Fig. S4 in ESI†); fluorescence spectra on JASCO spectroflurometer FP-8300 (Fig. S4 in ESI†) and mass spectra were recorded by HR-MS on the Bruker daltonic GmbH (Fig. S5 and Fig. S6 in ESI†). Melting points of all compounds are determined with METTLER which were further corrected using the TA Q2000 differential scanning calorimeter (DSC) (Fig. S7 and Fig. S8 in ESI†). Subsequently ^{1}H, ^{13}C NMR and 2D gHSQCAD in $CDCl_3$ were measured on the Varian mercury 500 MHz NMR using the tetramethylsilane as an internal reference (Fig. S9 and Fig. S10 in ESI†). Elemental analysis was carried out on the Elementar Vario EL III.

2.2. Synthesis of **1** and **2**

Vitamin K3 (2-methyl-1,4-naphthoquinone) 5.81 mmol (1 g) was dissolved in 25 ml dry methanol. The solution obtained by dissolution of the 5-nitro aminophenol (0.894 g for **1**) and 4-nitro aminophenol (0.894 g for **2**) in 15 ml of the dry methanol stirred for 30 min. The amino phenol solutions were added drop wise in the solution of Vitamin K3, and the reaction mixture was refluxed (Scheme 1). The reactions were monitored using thin layer chromatography and the products on plates visualized in the UV chamber. On completion of reaction the reaction mixture was dried at the room temperature (26 °C) for several days. The product(s) thus obtained were dissolved in toluene and purified using column chromatography 9:0.5 (Toluene: Methanol) 5% methanol in toluene which was eluent. A major product that reveals fluorescent orange band was separated. The solvent was reduced by rotatary evaporation and last 20 ml fractions were evaporated at the room temperature (26 °C). X-ray quality dark orange colored needle crystals were obtained.

2.3. Characterization of 6-methyl-9-nitro-5H-benzo[a]phenoxazin-5-one; **1**

Yellow crystal, Yield: 0.40 g (50%), m. p. 264.18 °C. Anal. data. Calc. for $C_{17}H_{10}N_2O_4$: C, 66.67; H, 3.29; N, 9.15. Found; C, 66.73; H, 3.26, N, 9.35. FT-IR (KBr; ν_{max} (cm^{-1}): 3108, 2921, 1628, 1579, 1525, 1338, 1230, 1096, 962, 828, 522. ^{1}H NMR (500 MHz, $CDCl_3$, δ (ppm): 2.26 (s, 3H), 8.70 (1H, d, J = 8.50 Hz, 8.318 (1H, d, J = 8.00 Hz), 8.184 (1H, m, J = 7.00 Hz), 8.174 (1 H, m, J = 7.00 Hz), 7.709 (1 H, s), 7.804 (1 H, d, J = 7.00 Hz), 7.785 (1 H, d, J = 7.00 Hz).^{13}C NMR (125 MHz, $CDCl_3$, δ (ppm)): C(1) = 126.63, C(2) = 132.50, C(3) = 133.02, C(4) = 125.31, C(4A) = 132.01, C(5) = 183.61, C(6) = 118.56, C(6A) = 144.62, C(7A) = 137.22, C(8) = 111.93, C(9) = 148.09, C(10) = 120.10, C(11) = 130.19, C(11A) = 150.82, C(12A) = 146.85, C(12B) = 130.58. UV–Vis; (λ_{max} (nm), DMSO): 366, 384, 477. Fluorescence (λ_{max} (nm), DMSO): 555. GC-MS (EI) *m/z*: 306 (M^{+}+H).

2.4. Characterization of 6-methyl-10-nitro-5H-benzo[a] phenoxazin-5-one; **2**

Dark yellow crystal, Yield: 0.55 g (80%), m.p. 235.81 °C. Anal. data. Calc. for $C_{17}H_{10}N_2O_4$: C, 66.67; H, 3.29; N, 9.15. Found; C, 66.76; H, 3.57, N, 9.07. FT-IR (KBr, ν_{max} (cm^{-1})): 3099, 2958, 2848, 1639, 1599, 1523, 1458, 1338, 1261, 1078, 1024, 968, 896, 833, 734,

Table 1
Crystallographic data of **1** and **2**.

Identification code	**1**	**2**
Empirical formula	C_{17} H_{10} N_2 O_4	C_{17} H_{10} N_2 O_4
Formula weight	306.27	306.27
Temperature	296(2) K	296(2) K
Wavelength	0.71073 Å	0.71073 Å
Crystal system	Monoclinic	Monoclinic
Space group	C 2/c	P 2_1/c
Unit cell dimensions	a = 13.4920(11) Å, b = 15.1908(12) Å, c = 13.6607(15) Å, α = 90°. β = 103.958(3) °. γ = 90°.	a = 10.5028(7) Å, b = 15.4190(10) Å c = 8.4959(5) Å α = 90°. β = 101.773(4) °. γ = 90°.
Volume	2717.1(4) $Å^3$	1346.91(15) $Å^3$
Z	8	4
Density(calculated)	1.497 Mg/m^3	1.510 Mg/m^3
Absorption coefficient	0.109 mm^{-1}	0.110 mm^{-1}
F(000)	1264	632
Theta range for data collection	2.781–28.359°.	2.783–28.346°.
Index ranges	−18 ≤ h<=17, −20 ≤ k<=20, −18 ≤ l<=18	−13 ≤ h<=14, −19 ≤ k<=20, −11 ≤ l<=11
Reflections collected	14209	10299
Independent reflections	3369 [R(int) = 0.1063]	3316 [R(int) = 0.0569]
Completeness to theta = 25.242°	99.7%	99.4%
Max. and min. Transmission	0.975 and 0.981	0.980 and 0.968
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	3369/0/209	3316/0/209
Goodness-of-fit on F^2	0.983	1.456
Final R indices [I > 2sigma(I)]	R1 = 0.0714, w*R2* = 0.1290	R1 = 0.0654, w*R2* = 0.0851
R indices (all data)	R1 = 0.2088, w*R2* = 0.1768	R1 = 0.1731, w*R2* = 0.0961
Extinction coefficient	n/a	n/a
Largest diff. peak and hole	0.276 and −0.371 e.$Å^{-3}$	0.243 and −0.282 e.$Å^{-3}$