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ASSESSMENTS OF ELECTRONIC PROPERTIES IN PHENOTHIAZINE CARBALDEHYDE REGIOISOMERS SERIES

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ABSTRACT. Regioselective C-formylation of phenothiazine using N,N-dimethylformamide is revisited and optimized synthesis of 10-methyl-10*H*phenothiazine-carbaldehyde regioisomers are presented. Recorded NMR and UV-Vis spectroscopic data are compared in the regioisomers series. Fluorescence emissions in the visible range are described. Density Functional Theory (DFT) computational results regarding structural characteristics in the regioisomers series are supporting the recorded spectral properties.

Keywords: *Phenothiazine carbaldehyde, UV-Vis absorption, Fluorescence, DFT.*

INTRODUCTION

Phenothiazine is a redox-active compound well known as a potent pharmacophoric group for medicinal applications [1], but also a suitable building block for new materials mainly based on UV-Vis absorption and fluorescence emission properties modulated by carrefully selected substitution patterns [2]. In this context, phenothiazine carbaldehide derivatives appear as versatile substrates for extending the functionalization of the parent heterocyclic unit. Literature survey indicate the phenothiazine-3-carbaldehyde as the most widely employed precursor mainly because it can be readily prepared by rather simple Vilsmeyer [3], or Duff [4] formylation procedures. Even though the preparation of phenothiazine-1-, 2-, and 4-carbaldehyde regioisomers was also previously reported, these regioisomers were less employed as precursors for further functionalization of phenothiazine unit.

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The Vilsmeier-Haack formylation of a phenothiazine substrate is based on aromatic electrophilic substitution reaction directed by the electron donor effect of the heterocyclic N atom mainly increasing the electron density in the *para* position of the adjacent aromatic ring. This procedure was first applied to 10-methyl-phenothiazine substrate and generated 3-formyl-10-methyl-phenothiazine in up to 50% yields [5]. Convenient formylation conditions were described for the preparation of 3-formyl-10-methyl-phenothiazine and 3,7-diformyl-10-methyl-phenothiazine using N,N-dimethylformamide (DMF) and phosphorous(V)oxychloride for generating the electrophile [6]. A modified procedure gave 97% yield 10-ethyl-3-formyl-phenothiazine when using chloroform solvent [7]

The microwaves assisted Duff formylation procedure using urotropine in acetic acid showed regioselectivity for position 3 and gave satisfactory results in the formylation of both phenothiazine and 10-methyl-phenothiazine substrates with less environmental burden [8].

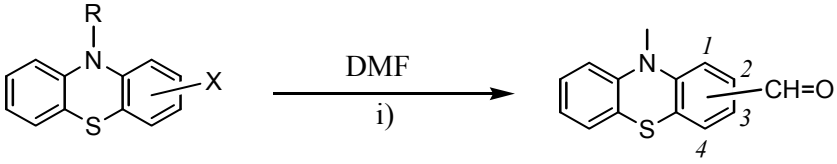
Lithiation and subsequent formylation using DMF as electrophile is another method designated to the preparation of heteroaromatic aldehydes bearing a formyl group adjacent to the heteroatom. When subjected to this procedure, phenothiazine may generate both C^1 (*ortho* to the N directing atom) and C^4 (*ortho* to the S directing atom) substitution products [9]. However a preference for substitution in the position *ortho* to the heterocyclic nitrogen atom was observed in the case of 10*H*-phenothiazine. A double lithiation experiment indicate the C^1 substited product in the presence of DMF, but other electrophiles such as acetyl chloride gave the N substited product [10]. An ingenious two step procedure was developed based on the formation of an unstable carbamate intermediate which favorize C^1-lithiation and generate the electrophilic substitution product exclusively at the carbon center [11] When sterically hindred N-methylformanilide was employed, 4-formyl-phenothiazine was preferentially formed [12]. 10-alkyl-phenothiazines appeared to undergo lithiation at position C^4 when using butyl lithium in the presence of TMEDA [13]. This strategy can be applied for the introduction of a formyl group at position C^3 of the phenothiazine core only based on a halogen-litium exchange reaction applied to a halogenated phenothiazine substrate followed by subsequent treatment with DMF electrophyle [14].

In this work, the regioselective C-formylation of phenothiazine substrate in the presence of DMF was achieved by modulating the chemical reactivity of the heterocycle towards electrophilic substitution and optimal experimental conditions are described. The electronic properties of the prepared C-formyl-N-methyl-phenothiazine regioisomers were discussed based on NMR and UV-Vis absorption/emission spectroscopic data recorded in solution. Theoretical computational data were employed in supporting the fine tunable electronic properties in the regioisomers series.

RESULTS AND DISCUSSIONS

Synthesis of 10-Methyl-phenothiazine carbaldehyde regioisomers

10-Methyl-10*H*phenothiazine-1-, 2- and 4-carbaldehyde regioisomers **1, 2, 4** were successfully obtained by a two-steps procedure involving a phenothiazine-lithium intermediate further trapped by the treatment with dimethylformamide (DMF) electrophile. A careful selection of the reaction conditions (substrate, lithium reagent, reaction temperature) was required in order to obtain satisfactory yields of each target regioisomer (scheme 1). Thus, when starting with N-methyl-phenothiazine substrate and *n*-BuLi reagent a hydrogen lithium exchange occurred at 0 ^{o}C preferentially under the *orto* directing effect of the heterocyclic sulfur atom (affording phenothiazine-4-carbaldehyde **4** in 43% yields). At 0 ^{o}C the nitrogen *orto* directing effect was prevalent in the 10H-phenothiazine substrate and the sterically hindered 10-methyl-phenothiazine-1-carbaldehyde **1** was obtained in 25% yield after a subsequent alkylation of the 1-formyl-10Hphenothiazine intermediate. The preparation of phenothiazine 2-carbaldehyde **2** was best achieved by subjecting 2-chloro-10-methyl-phenothiazine substrate to halogen-lithium exchange using metallic lithium under sonochemical conditions in the presence of DMF. 10-Methyl-10*H*phenothiazine-3-carbaldehyde was obtained in 80% yields by an adapted Vilsmeyer procedure using 1,2-dichloroethane solvent.



R=H, X=H,	i) *n*BuLi/Et_2O 0^{o}C, ii) NaH/THF, H_3C-I	**1** *1*-CHO 22%
R=Me, X= Cl	i) Li/Et_2O,))), 30 ^{o}C, 6h	**2** *2*-CHO 43%
R=Me, X=H	i) $POCl_3$/DCE, 90 ^{o}C, 6h	**3** *3*-CHO 80%
R=Me, X=H	i) TMEDA/*n*Bu-Li,r.t.,20 min	**4** *4*-CHO 61%

Scheme 1. *Regioselective C-formylation of 10Hphenothiazine derivatives.*

The recorded ^{1}H-NMR spectra are collectively presented in figure 1 for regioisomers **1-4**, thus giving the possibility of inspecting the key signals and comparing the deshielding effects induced by electronic conjugation, steric hindrance and magnetic anisotropy of the aldehyde group.

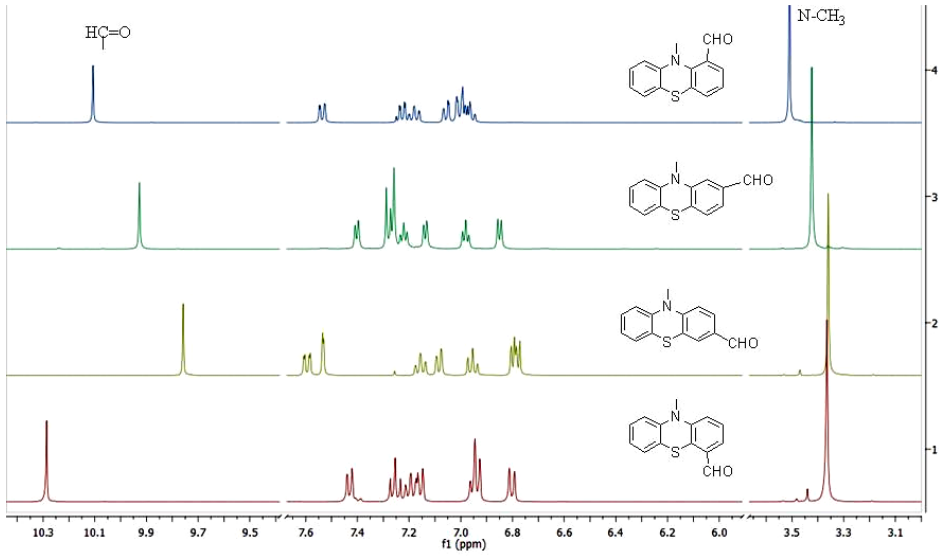


Figure 1. 400 MHz ^{1}H-NMR spectra of 10-methyl-10-*H*phenothiazine-carbaldehyde regioisomers in $CDCl_3$ (from top to bottom: **1, 2, 3, 4**) in $CDCl_3$

Electronic properties

The molecular structures of the regioisomesr **1-4** have been studied by using density functional theory. The energies corresponding to the optimized geometries (E) in ground states and frontier molecular orbitals (E_{HOMO}, E_{LUMO}) were computed at the using Spartan programme [15] and the results are presented in Table 1.

Taking into consideration the calculated E values (Table 1) the stability of regioisomers **1-4** may be correlated to the substitution pattern of the phenothiazine unit and falls in the order: phenothiazin-1-< 4-< 2-< 3-yl in concordance with a steric hindrance in positions 1 of the heterocycle and favourable extended n-π conjugation in position 2, or 3 respectively.

The frontier molecular orbital plots presented in figure 2 show a participation to the HOMO of all the atoms joint in the heterocyclic system, while LUMO appears localized on the formyl substituent and its adjacent benzene ring with a selective participation of the heteroatoms according to the substitution pattern (N atomic orbitals participates to LUMO in the case of **1** and **3**, while S atomic orbitals participates to LUMO in the case of **2** and **4** regioisomers).

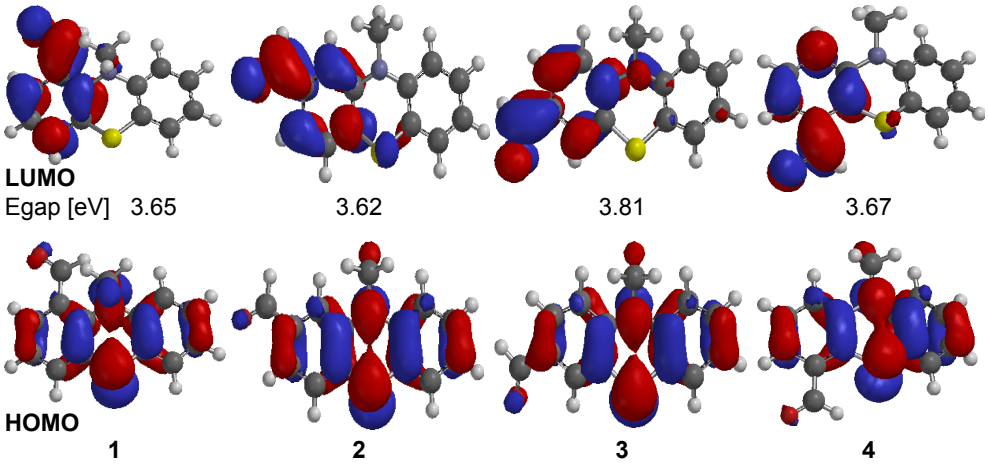


Figure 2. Frontier molecular orbital plots of
10-methyl-phenothiazine-carbaldehyde regioisomers

Each phenothiazine carbaldehyde **1-4** show two absorption bands, situated in the UV region (Table 1) with larger extinction coefficients for the higher frequency band which can be assigned to allowed π→π* transitions involving the excitation of the electrons from the aromatic rings; the forbidden n→π* transitions may be responsible for the low intensity band situated at longer wavelengths. These absorption bands appear slightly affected by the position of the auxochrome formyl group, except for the case of **3** which reveals a hypsochromic shift of aprox. 30 nm for the band situated at longer wavelength (Table 1); in agreement with this experimental evidence **3** is also characterized by the largest computed HOMO-LUMO energy gap of the series (figure 2).

Upon excitation with either of the two UV absorption maxima, each regioisomer **1-4** exhibited emission bands in solution with maxima situated in the visible region (figure 3). A correlation between the position of the emission band and the substitution pattern of the heterocycle indicate a red shift of the emission maxima according to the auxochrome position in the following order: phenothiazine-1yl-<2-yl<-3-yl<-4-yl-carbaldehyde. Larger Stokes shift values are noticeable in the case of **1** and **3** which can be correlated to geometrical changes upon excitation, from a non-planar ground-state of the phenothiazine moiety to a largely planarized excited state [16] and corroborated with computational results regarding LUMO electron distribution (figure 2).

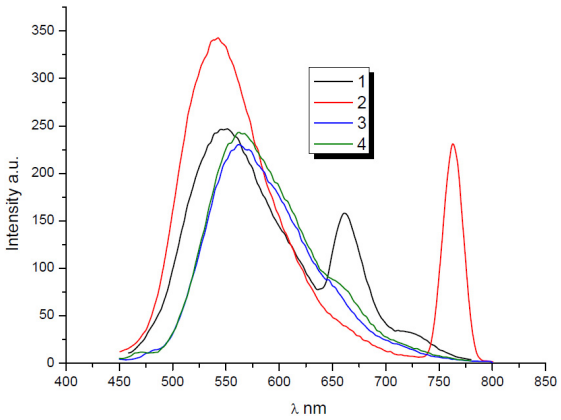


Figure 3. Fluorescence emission spectra of 10-methyl-10*H*phenothiazine carbaldehyde regioisomers **1-4** in 0.02mM in DCM.

Table 1. Electronic properties of phenothiazine carbaldehyde **1-4** determined by UV-Vis absorption/emission spectroscopy 10^{-4} M in DCM and molecular modelling

Cpd	$\lambda_{max, abs}$ (ε) [nm]	$\lambda_{max, em}$ [nm]	Stokes shift [cm^{-1}]	E_{HOMO} [eV]	E_{LUMO} [eV]	E [hartree]
1	277 (54400) 411 (3180)	543 670	9400	-5.25	-1.60	-1068.264
2	282 (109200) 418 (4730)	551, 730	5700	-5.35	-1.73	-1068.274
3	282 (60950) 381 (5900)	567	8600	-5.37	-1.56	-1068.275
4	277 (58600) 419 (6170)	571	6300	-5.37	-1.70	-1068.269

CONCLUSIONS

Adequate experimental conditions for regioselective C-formylation of 10-methyl-10*H*-phenothiazine substrate were described.

Evidences of photophysical properties of phenothiazine carbaldehyde regioisomers were brought by means of UV-Vis absorption/emission spectroscopy which indicated fine tunable absorptions in the UV region and fluorescence emission in visible region according to the position of the formyl auxochrome.

EXPERIMENTAL SECTION

*10-methyl-10Hphenothiazin-1-carbaldehyde (**1**).*

a) To a solution of phenothiazine (4 g, 20 mmol) in 150 ml of dry ethyl ether *n*-BuLi (31 ml 25 mmol, 1.6 M in hexane) was added under argon atmosphere at 0°C. The reaction mixture was stirred 10 hours at room temperature and then DMF (1.5 g, 20 mmol, 0.944 g/cm^3) was added drop wise at 0°C. After it was stirred one hour at room temperature, the reaction mixture was hydrolyzed with ice cold aqueous HCl 0.5 N. The mixture was shaken vigorously and the organic layer was then separated. The aqueous phase was extracted three times with ethyl ether (50 ml). The organic phases were collected, washed with water and dryed ower magnesium sulfate. After the evaporation of the solvent under vacuum, the red viscous residue was purified by column chromatography (silica gel, hexane/ethyl acetate= 10/1) to give 10Hphenothiazin-1-carbaldehyde 1.14g (25%) m.p.= 81-82°C, (lit. 81-83°C [12])

b) To a suspension of NaH (0.174 g, 4.4 mmol) in dry THF (20 ml) was added under continuous stirring, a solution of 10H-phenothiazine-1-carbaldehyde (1g 4.4 mmol) in 10 ml dry THF (under inert atmosphere). The mixture was stirred for 4h, at 0-5°C. To the obtained solution, was added methyl iodide (0.62g, 4.4 mmol 2.28 g/cm^3) and the mixture was stirred at room temperature for 10 hours. The reaction mixture was treated with 100 ml water and extracted three times with ethyl ether (30ml). The organic phase was collected and dryed over magnesium sulfate. After evaporation of the organic solvent the crude product was purified by column chromatography (silica gel, hexane/ethyl acetate= 10/1) to give (0.95 g 90%) yellow powder m.p.= 75-77°C, (lit. 70-71°C [17])

δ_H (300 MHz, $CDCl_3$) 3.62 (3H, s, CH_3), 6.85 (1H, d, *J* 7.8 Hz, H_9), 7.00 (1H, td, *J* 7.5, 1.9 Hz, H_7), 7.07-7.13 (2H, m, H_6, H_8), 7.14 (1H, dd, *J* 2.0, 7.8 Hz, H_4,), 7.28 (1H, t, *J* 7.8 Hz, H_3,), 7.43 (1H, dd, *J* 2.0, 7.6 Hz, H_2), 9.56 (1H, s, CHO); δ_C (75 MHz, $CDCl_3$) 43.9, 118.4, 122.6, 124.1, 125.6, 126.5, 126.6, 127.6, 130.6, 131.1, 131.3, 146.4, 146.8, 189.7; MS m/z (EI, 70eV) 241 (M^+).

*10-methyl-10Hphenothiazin-2-carbaldehyde (**2**).*

10-methyl-2-chloro-10*H*phenothiazine (247 mg, 1 mmol) was solved in dry diethyl ether (25ml) under inert atmosphere, metallic lithium (7 mg, mmol) and dry dimethylformamide (146 mL, 2 mmol) were added. The reaction mixture was sonicated in an ultrasonic bath at 30°C for 6h. The mixture was poured into ice (50 g), and then extracted with dichloromethane and the two layers were separated; after evaporation of the organic solvent the crude product was purified by column chromatography with toluene as eluent. Yellow-brown powder (103.6 mg, 43%), mp 69-71°C, (lit bp 220°C/3 torr [18]);

δ_H (600 MHz, $CDCl_3$) 3.39 (3H, s, CH_3), 6.82 (1H, d, *J* 8.1Hz, H_9), 6.95 (1H, t, *J* 7.4Hz, H_7), 7.11 (1H, d, *J* 7.5Hz, H_6), 7.19 (1H, t, *J* 7.4 Hz, H_8), 7.23-7.24 (2H, m, H_1, H_4), 7.37 (1H, d, *J* 7.6 Hz, H_3), 9.89 (s, 1H, CHO); δ_C (150 MHz) 35.5, 112.2, 114.6, 121.9, 123.0, 125.8, 127.2, 128.1(2C), 132.6, 135.9, 144.9, 146.4, 191.6; MS m/z (EI, 70eV), 241 ($M^{+\cdot}$).

*10-methyl-10Hphenothiazin-3-carbaldehyde (**3**)*

DMF (24 mmol) was cooled to 0°C, then $POCl_3$ (24 mmol) was added drop wise and the mixture was stirred at room temperature for one hour. A solution of 10-methyl-10*H*-phenothiazine (20 mmol) dissolved in 1,2-dichloroethane (30 ml) was added slowly and the reaction mixture was stirred at 90°C for 6 hours. After cooling, an ice cold saturated solution of sodium acetate (30 ml) was added drop wise to the reaction mixture. The product was extracted with ethyl acetate, and the extract was dried over magnesium sulfate and then concentrated to dryness.

Yellow precipitate recrystallized from toluene (3.85g, 80%), mp 88°C lit 81-82 [19]; δ_H (600 MHz, $CDCl_3$) 3.36 (s, 3H), 6.78 (1H, d, *J* 8.0 Hz, H_9), 6.80 (1H, d, *J* 8.4 Hz, H_1), 6.95 (1H, t, *J* 8.4 Hz, H_7), 7.08 (1H, dd, *J* 1.4, 7.6 Hz, H_6), 7.15 (1H, td, *J* 1.4, 8.4 Hz, H_8),7.53 (1H, d, *J* 2 Hz, H_4), 7.60 (1H, dd, *J* 2.0, 8.4 Hz, H_2), 9.76 (1H, s, CHO); δ_C (150 MHz, $CDCl_3$) 35.8, 113.7, 114.8, 122.4, 123.6 123.8, 127.2, 127.8, 130.5, 131.1, 144.0, 150.9, 190.0; m/z (EI, 70eV) 241 ($M^{+\cdot}$).

*10-methyl-10Hphenothiazin-4-carbaldehyde (**4**)*

10-methylphenothiazine (2 g, 8.8 mmol) was dissolved in dry ethyl ether (50 cm^3). After 10 min under argon atmosphere, TMEDA (3.32 cm^3, 22 mmol) was added followed by *n*-butyllithium (13.8 cm^3 of a 1.6 M solution in hexane, 22 mmol). The mixture was kept at room temperature for 0.5 h, then cooled at 0°C before dry DMF (1.6 g, 0.948 g/cm^3, 22 mmol) was added. The mixture was stirred for 20 min at room temperature. The reaction mixture was poured into cooled aqueous HCl (4.5% w/v; 180 cm^3) and further stired for 30 min. The organic phase was separated and the aqueous phase was extracted with chloroform (3x100 cm^3). The combined organic phases were dried and evaporated to give an orange oil. The crude product was subjected to column chromatography (silica gel, hexane/ethyl acetate=8/1), yellow crystals (1.38 g, 61%) mp 110-112°C (lit. 110-111°C [20])

Yellow crystals, (0.97g, 43%), mp 110-112°C (lit[13], 110-111°C); δ_H (600 MHz, $CDCl_3$) δ 3.46 (s, 3H, CH_3), 6.89 (1H, d, *J* 8.1 Hz, H_9), 6.95 (1H, t, *J* 7.8 Hz, H_7), 7.03 (1H, d, *J* 7.8 Hz, H_1), 7.17-7.21 (2H, m, H_6, H_8), 7.28 (1H, t, *J* 7.8 Hz, H_2), 10.31 (1H, s, CHO); δ_C (150 MHz, $CDCl_3$) 36.5, 115.3, 119.8, 122.8, 123.6, 124.5, 126.7, 127.7, 127.9, 130.4, 133.0, 145.2, 145.9, 190.4. m/z (EI, 70eV) 241 ($M^{+\cdot}$), 226.

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