New Hydrazyl Derivatives with Multiple Properties

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Received August 17, 2009: Revised December 10, 2009: Accepted December 31, 2009

Abstract: 4-(N',N'-diphenylhydrazino)-3,5-dinitrobenzoic acid in reaction with 4-hydroxy-tempo, 4-aminobenzo-15crown-5, and 1-bromoacetyl-pyrene, yielded the corresponding esters or amides, as yellow compounds. These hydrazines, by oxidation with lead dioxide, converted into the stable hydrazyl free radicals, with a purple-violet color. Same yellow hydrazines in reaction with alkali bases are converted into the corresponding salt of green color. The newly synthesized compounds were characterized by elemental analysis, IR, UV-Vis, ¹H- and ¹³C-NMR, and EPR (where applicable). Acidbase, redox, fluorescence and complexation properties were also studied and discussed.

Keywords: Hydrazyl, radical, tempo, crown, pyrene, EPR.

INTRODUCTION

Hydrazyl radicals are one of the most known types of stable free radicals under usual conditions [1]. Besides their great stability, they have a range of different properties, such as acid-base and redox behavior [2]. Because all these properties are accompanied by color changes, hydrazyl radicals have been employed as sensors and probes in different physico-chemical processes, making them to be followed very easily even with naked eyes [3, 4].

If such compounds are covalently bonded to other materials of interest, such are crown ethers, nitroxide radicals, fluorescent derivatives, and so on, multifunctional derivatives are obtained. These derivatives represent a challenge in the area of organic compounds with multiple applications.

Nitroxide radicals are usually employed as probes in different systems, from biological ones to polymer chemistry [5]. Crown ethers derivatives are compounds, which exhibit strong complexation properties, useful not only in analytical chemistry, but also in membrane transport or in interphasic catalysis [6]. Fluorescent derivatives are very important in medicine, biology and biochemistry [7]. Hydrazyl or hydrazine derivatives modified with such compounds will have a great interest for many chemists.

In our work we present the synthesis of some new derivatives with multiple properties, such as acid-base, redox, complexation and fluorescence. All the new compounds were characterized by appropriate spectral and physico-chemical means.

RESULTS AND DISCUSSION

Synthesis of the Compounds 1-9 and their Main Physico-Chemical Properties

Starting from the dinitrobenzoic acid derivative and using simple coupling reactions, it was possible to obtain the compounds 1-3, Fig. (1), with good yields. Thus, carboxylic group easily reacts with the hydroxyl group from 4-hydroxytempo in the presence of dicyclocarbodiimide (DCC), to form the ester 1; with the amino-group from 4-aminobenzo-15-crown-5, to form amide 2 (as well in the presence of DCC), and, with 1-bromoacetyl-pyrene, to form ester 3, in the presence of a base. General yields were around 40-60%, and the new compounds 1-3 were separated and purified by preparative TLC. Characterization of these compounds was performed usually in the first instance by ¹H-and ¹³C-NMR (not suitable for the free radicals), elemental analysis and IR. All these data confirm the chemical structure of the compounds, as well as their purity. Multiple properties, such as color, fluorescence, radical behavior, complexation, etc, will be detailed as appropriate.

As many other congeners, hydrazines [1-4], compounds 1-3 exhibit the same properties: i) by oxidation, they are converted into the corresponding stable hydrazyl radicals 4-6, (Scheme 1), and ii) in basic media, the acidic hydrazine hydrogen atom is removed, with the formation of the corresponding salts 7-9. All these acid-base and redox processes are accompanied by color change, see (Scheme 1) or Experimental part.

EPR Spectra of the Compounds 1, 4-6

Hydrazyl radicals are mainly characterized by their hyperfine coupling constants, due to the interaction of the unpaired electron with the two nitrogen atoms from the hydrazine moiety. Due also to a 'push-pull' effect, they are quite stable under usual condition, with no decomposition, dimerization and no reaction with oxygen air being noticed [1, 2].

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Fig. (1). Structure of the compounds 1-3.



Scheme 1. Acid-base and redox behavior of the compounds 1-9, accompanied by color changes.

Compound 1 is in fact a nitroxide derivative, Fig. (1) and its EPR spectrum consists of only 3 lines, Fig. (2a), with a hyperfine coupling constant a_N of 15.40 G (due to the interaction of the unpaired electron with only one nitrogen atom). By oxidation, compounds **1-3** are converted into the corresponding hydrazyl radicals **4-6** (**4** being now in fact a diradical), see Scheme **1**. The EPR spectrum of the diradical **4** is shown in Fig. (**2b**). It consists of a superposition of a



Fig. (2). Experimental (a-c) and simulated EPR spectra (d-e).



Fig. (3). Formation of a supramolecular complex.

nitroxide type spectrum and a hydrazyl type spectrum, in which the hyperfine coupling constants are quite different $(a_{N1}=15.4 \text{ G}, a_{N2}=12.6 \text{ G} \text{ and } a_{N3}=4.3 \text{ G})$. Compounds **5** and **6** have a very similar spectrum, showed in Fig. (**2c**). All these EPR spectra can be well simulated; Fig. (**2d-e**) shows the simulated spectra obtained using *WinSim* software [8].

Complexation Properties of Compound 2

Crown ethers have good complexation properties towards alkali cations [3]. In order to test our compound 2 (which contains a 15-crown-5 moiety) as a complexing agent for the alkali cations lithium, sodium, and potassium, we used the well known method of Job's curve [9]. This is possible because the formation of the complex is accompanied by a colour change, Fig. (3). The ratio of the complexation between these alkali cations and compound 2 has been established (by Job's curve, see Experimental) to be 1 to 1.

Fluorescence Properties of Compound 3

Pyrene derivatives are well known as fluorescence precursors, so our derivative exhibited the expected fluorescence property [7]. Thus, excitation at 330 nm leads to the obtaining of fluorescence with a maximum intensity at around 420 nm. The typical spectrum is shown in Fig. (4). As usual in the case of free radicals linked to fluorescence derivatives, for compound $\mathbf{6}$, the intensity of the fluorescence is lower.



Fig. (4). Fluorescence spectrum of the compound 3.

In conclusion, all the new synthesized compounds exhibit multiple properties; thus, they might be involved in acidbase, redox, complexation and fluorescence studies. Most of the changes that occur in such processes can be followed just by naked eyes, due to the color changes that appear in such processes.



EXPERIMENTAL

Starting materials were archived from Sigma-Aldrich and used as received. Solvents were purchased from Chimopar and used as received. IR spectra were recorded on a Bruker Vertex 70 spectrometer, NMR spectra were recorded on a Bruker BB300 instrument, EPR spectra on Jeol JES-FA100 spectrometer, and UV-Vis spectra on a UVD-3500 spectrometer. Simulations of the EPR spectra were performed using the *WinSim* free software [8]. Typical settings used for the EPR measurements are as follows: concentration of the sample 10⁻⁴ M, number of scans 1, centre field 3360 G, sweep field 100 G, frequency 9.42 GHz, power 1mW, sweep time 60 s, time constant 0.1 s, modulation frequency 100 kHz, gain 100, and modulation width 1G.

1. 394 mg (1 mmol) of 4-(N',N'-diphenylhydrazino)-3,5dinitrobenzoic acid (synthesized as previously described [10]), was dissolved into 50 mL dry DCM 172 mg of 4hydroxy-tempo (1 mmol) and 250 mg DCC (1.2 mmol) were then added, and the mixture was left for 2 days at room temperature. After the solvent removal, the residue has been chromatographed on preparative TLC (silica gel) twice, using DCM/MeOH 9/1 as eluent. Yields were about 40%. Elemental analysis: Theoretical: $C_{28}H_{30}N_5O_7$ M=548, C=61.31%, H=5.51%, N=12.77%; Found: C=61.01%, H=5.59%, N=12.22%.

FT-IR (ATR in solid, v cm⁻¹): 3295m; 3062w; 2928m; 2854m; 1703s; 1621vs; 1534vs; 1489vs; 1342m; 1264s; 1154m; 751m; 691m.

UV-Vis (DCM, λ nm): 383; by oxidation with lead dioxide 505 (200 mg lead dioxide for 5 mg compound); in basic media 623.

EPR (DCM): $a_N=15.4$ G; by oxidation with lead dioxide (200 mg lead dioxide for 5 mg compound) $a_{N1}=15.4$ G, $a_{N2}=12.6$ G and $a_{N3}=4.3$ G.

2. 394 mg (1 mmol) of 4-(N',N'-diphenylhydrazino)-3,5dinitrobenzoic acid was dissolved into 100 mL DCM, 280 mg of 4-aminobenzo-15-crown-5 (1 mmol) and 230 mg DCC (1.1 mmol) were added, and the mixture was left overnight at room temperature. Next day the mixture was washed with an aqueous solution of hydrochloric acid (0.1 M), sodium bicarbonate (3%) and water. After separation, the organic phase was dried over anhydrous sodium sulfate, and the solvent was removed. The residue was chromatographed on preparative TLC (silica gel) twice, using DCM/MeOH 9/1 as eluent. Yields were about 60%. Elemental analysis: Theoretical: $C_{33}H_{33}N_5O_{10}$ M=659, C=60.09%, H=5.04%, N=10.62%; found: C=60.27%, H=5.14%, N=10.55%. ¹H-NMR (CDCl₃, δ ppm, *J* Hz): 9.82(s, 1H, NH, deuterable); 9.39(bs, 1H, NHCO); 8.90(bs, 1H, H-5 or H-3); 8.49(bs, 1H, H-5 or H-3); 7.34(m, 1H, H-21); 7.32(dd, 4H-*meta*, H-9, H-11, H-15, H-17, 8.4, 7.6); 7.14(tt, 2H-*para*, H-10, H-16, 7.6, 1.2); 7.12(dd, 4H-*ortho*, H-8, H-12, H-14, H-18, 8.4, 1.2); 7.12(m, 1H, H-25); 6.68(d, 1H, H-22, 8.4); 4.02(t, 4H, H-29, H-30, 6.1); 3.85÷3.70(m, 12H, H-26÷H-28, H-30÷H-33).

¹³C-NMR (CDCl₃, δ ppm): 161.49(C-19); 156.87(Cq); 148.53(Cq); 146.55(C-7, C-9); 145.60(Cq); 139.94(Cq); 131.96(Cq); 129.37(C-*meta*, C-9, C-11, C-15, C-17); 125.30 (C-*para*, C-10, C-16); 124.43(Cq); 120.49(C-*ortho*, C-8, C-12, C-14, C-18); 113.97(CH); 113.95(CH); 107.72(CH); 70.50(CH₂); 70.41(CH₂); 70.03(CH₂); 69.94(CH₂); 69.24 (CH₂); 69.04(CH₂); 68.91(CH₂); 68.34(CH₂).

FT-IR (ATR in solid, v cm⁻¹): 3298m; 3064w; 2927m; 2870m; 1623s; 1533vs; 1510vs; 1491vs; 1454m; 1425m; 1345m; 1258s; 1194m; 1130s; 1057w; 993w; 909m; 727m; 696m; 646w.

UV-Vis (DCM, λ nm): 412; by oxidation with lead dioxide 508 (200 mg lead dioxide for 5 mg compound); in basic media 628.

EPR (DCM): after oxidation with lead dioxide (200 mg lead dioxide for 5 mg compound), a_{NI} =9.4 G, a_{N2} =7.8 G.

3. 394 mg (1 mmol) of 4-(N',N'-diphenylhydrazino)-3,5dinitrobenzoic acid was dissolved into 70 mL DMF 323 mg of 1-bromoacetyl-pyrene (1 mmol) were added, and the mixture was stirred overnight in the presence of 3 g of sodium bicarbonate. Next day to the mixture was added 200mL of water, acidified at pH~5, and the solution extracted with DCM. The organic phase was dried over anhydrous sodium sulfate, and the solvent was removed. The residue was chromatographed on preparative TLC (silica gel) twice, using DCM/MeOH 9/1 as eluent. Yields were about 50%. Elemental analysis: Theoretical $C_{37}H_{24}N_4O_7$ M=636, C=69.81%, H=3.80%, N=8.80%; found: C=69.44%, H=3.80%, N=8.68%.

¹H-NMR (CDCl₃, δ ppm, *J* Hz): 9.96(s, 1H, NH, deuterable); 9.08(bs, 1H, H-3 or H-5); 9.01(d, 1H, H-34, 9.5); 8.42(bs, 1H, H-5 or H-3); 8.33(d, 1H, H-23, 8.1); 8.28÷8.25(m, 2H, H-5, H-7); 8.24(d, 1H, H-33, 9.5); 8.20(d, 1H, H-26 or H-27, 8.8); 8.19(d, 1H, H-24, 8.1); 8.08(d, 1H, H-30, 9.0); 8.06(d, 1H, H-26 or H-27, 8.8); 8.24(d, 1H, H-24, 9.4); 7.34(dd, 4H-*meta*, H-9, H-11, H-15, H-17, 8.4, 7.6); 7.18(tt, 2H-*para*, H-10, H-16, 7.6, 1.2); 7.14(dd, 4H-*ortho*, H-8, H-12, H-14, H-18, 8.4, 1.2); 5.73(s, 2H, H-20).

¹³C-NMR (CDCl₃, δ ppm): 194.83(C-21); 162.70(C-19); 146.49(C-7, C-13); 141.32(C-1); 134.74(Cq); 131.06(Cq); 130.55(Cq); 130.46(C-33); 130.31(C-26 or C-27); 129.48(Cmeta, C-9, C-11, C-15, C-17); 127.86(Cq); 127.03(C-30); 126.79(C-29, C-31); 126.70(C-24); 126.58(C-23); 125.78(Cpara, C-9, C-16); 125.12(C-36 or C-37); 124.45(C-34); 124.13(C-36 or C-37); 124.03(C-26 or C-27); 120.56(Cortho, C-8, C-12, C-14, C-18); 119.05(C-22); 68.74(C-20). FT-IR(ATR in solid, v cm⁻¹): 3276m; 3104w; 3047w; 2937w; 1732vs; 1676s; 1622s; 1588s; 1564m; 1528vs; 1488vs; 1457m; 1415s; 1380m; 1357m; 1257vs; 1215s; 1185s; 1151s; 1116s; 982m; 953m; 931m; 850s; 761m; 749m; 719s; 695m; 621m; 568w.

UV-Vis(DCM, λ nm): 395; by oxidation with lead dioxide 500 (200 mg lead dioxide for 5 mg compound); in basic media 593.

EPR (DCM): after oxidation with lead dioxide (200 mg lead dioxide for 5 mg compound), a_{N1} =9.4 G, a_{N2} =7.8 G

Determination of the Complexation Ratio by Job's Curve

Equimolar solution of compound **2** and lithium hydroxide, sodium hydroxide and potassium hydroxide in dry methanol was prepared. As a typical procedure, 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, and 1.8 mL of compound **2** was mixed with 1.8, 1.6, 1.4, 1.2, 1.0, 0.8, 0.6, 0.4 and 0.2 mL of the alkali solution, respectively, to achieve a total of 2 mL mixture each time. For each mixture, the absorbance was registered at 628 nm and plotted against concentration. The maximum of the absorbance had been recorded in the case of mixture formed by 1 mL compound **2** and 1 mL alkali hydroxide (lithium hydroxide, sodium hydroxide and potassium hydroxide), proving thus the ratio of 1 to 1 between the crown moiety and the cation.

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