Synthesis and structural characterization of a stable betaine imino-nitroxide free diradical

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Abstract

Starting from ready available compounds, a stable diradical of imino-nitroxide type has been synthesized in a multistep process. Structural characterization of the intermediates and final product included ^{1}H- and ^{13}C-NMR, elemental analysis, IR, UV-Vis and EPR spectroscopy. The stable diradical contains also a betaine structure with extended conjugation, which is responsible for its intense colour. Reduction of the stable betaine diradical led to a colour change from blue to yellow. The process is reversible, oxidation restoring the betaine diradical.

Keywords: Free radical, hydrazyl, EPR, betaine

Introduction

Hydrazyl free radicals are one the most studied class of paramagnetic compounds. Although they are known since 1922,[1] when Goldschmidt and Renn discovered the violet-coloured free stable radical 2,2-diphenyl-1-picrylhydrazyl (DPPH), hydrazyl free radicals are still widely used as EPR standard and as colorimetric reagent.[2-4]

Due to its stability and intense violet colour, it is quite useful in many investigations, including the measurements of antioxidant activities and polymerization processes.[5-7] In the same way, nitronyl-nitroxide and imino-nitroxide stable free radicals found applications in interesting processes, such as nitrogen oxides (NOx) detection and measurement.[8-10] Molecules containing more than one moiety of a stable radical are called polyradicals, and they are compounds of special interest, owing to their increased magnetic properties, and many of them are used as potential probes and sensors in physical, chemical, or biological processes.[11,12]

In materials chemistry, a recent and attractive field is organic-based magnetic materials.[13] This area of science offers the possibility to build step-by-step single molecules which contain

one or more free radical moieties. Co-operative magnetic properties may lead to the formation of a metallic organic solid, with important practical applications. By using the appropriate building blocks, the properties of these compounds may be tuned to achieve the desired interaction.

Pure organic materials based on stable polyradicals (stable organic high spin molecules) are known also in literature data.[14-16] Usually, their properties are related to ferromagnetism or other metallic properties.

Stable betaine diradical compounds derived from the DPPH stable free radicals are known since 1997;[17] these are intensely coloured compounds with multifunctional properties, such as redox and acid-base. In this work we describe a multistep synthesis which finally led to the obtaining of a stable betaine imino-nitroxide diradical, with multifunctional properties.

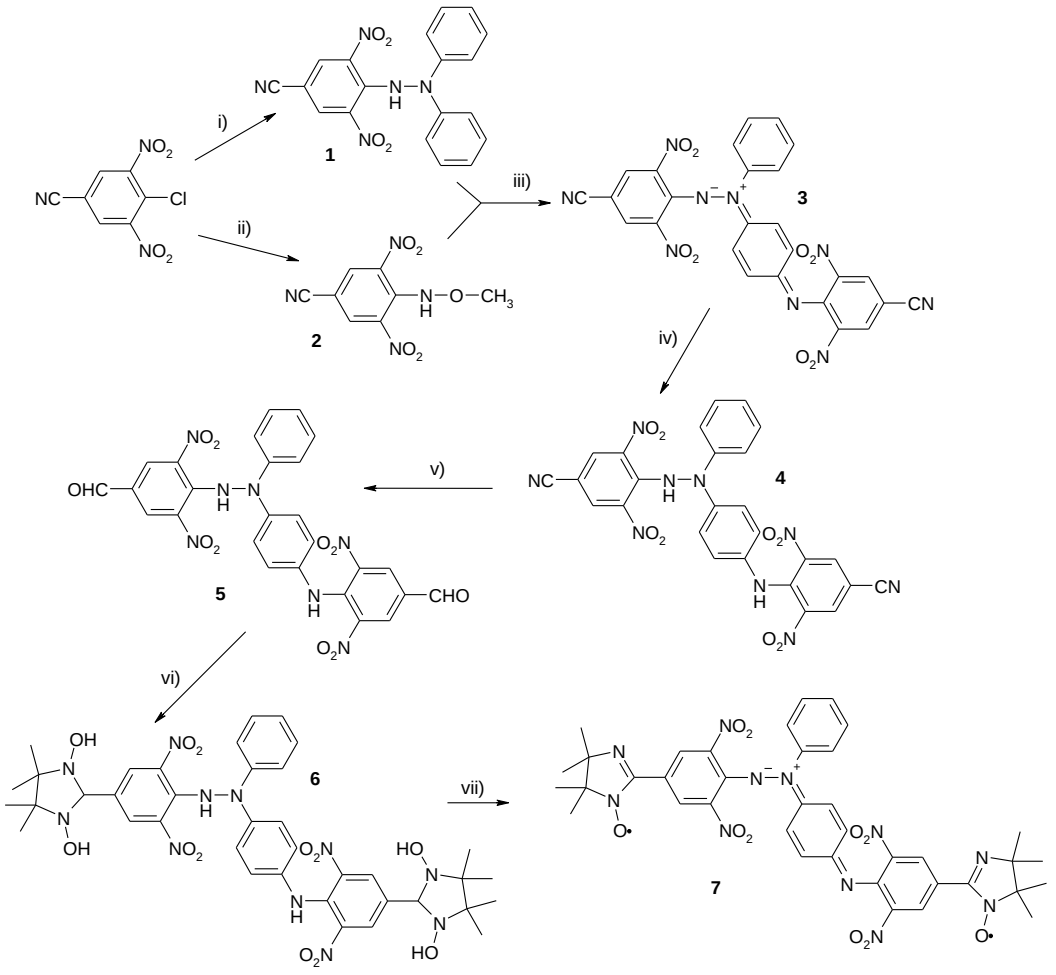

Figure 1. Synthesis of the stable betaine diradical **7**; (i) 1,1-diphenylhydrazine, ethanol, 2 h reflux; (ii) methoxyamine, ethanol, 2 h reflux; (iii) PbO_2, dichloromethane (DCM); (iv) ascorbic acid; (v) diisobutylaluminium hydride (DIBAL-H), DCM, -78 ^oC; vi) 2,3-bis(hydroxyamino)-2,3-dimethylbutane, DCM, 3 days; (vii) PbO_2, DCM.

Results and Discussion

Although the compounds **1-4** (Figure 1) are described in the literature,[17,19] in this work their synthesis has been improved. Thus, the reaction conditions (time, solvent, temperature) were optimized in order to get good yields and an easy way to afford the pure derivatives with minimal purification procedures. A key intermediary compound is the dialdehyde **5**, which is obtained from betaine **3** in a two step reduction process. Eventually, dialdehyde **5** led to the aimed stable diradical **7**.

The synthesis started from the commercially available 4-chloro-3,5-dinitrobenzonitrile, which on reaction with diphenylhydrazine and methoxyamine led to the compounds **1** and **2**, respectively (Figure 1). The betaine **3** is obtained by oxidation of an equimolar mixture of these with lead dioxide. Betaine **3** is reduced first to the corresponding hydrazine **4**, and then to the dialdehyde **5** by DIBAL-H. Treatment of **5** with 2,3-bis(hydroxyamino)-2,3-dimethylbutane led to the condensation product **6** (not isolated), which on oxidation is converted into the betaine diradical **7**.

In IR spectra, amino groups are present at about 3300 cm^{-1}, aromatic moieties at 3000-3100 cm^{-1}, nitro groups appear at *ca.* 1350 and 1550 cm^{-1}, aldehyde groups at *ca*. 1700 cm^{-1}, and the nitrile groups at *ca.* 2230 cm^{-1}. ^{1}H- and ^{13}C-NMR spectra confirmed also the structures of the obtained compounds (besides **7**, which was characterized by EPR); thus, amino groups are shifted under the influence of their chemical neighbors, and they appear between 10-11 ppm; carbonyl groups are present at ~ 10 ppm, and all other ^{1}H- and ^{13}C-NMR values confirmed the structure (see Experimental Section). The diradical **7** has been characterized by EPR spectroscopy; Figure 2 shows the recorded spectrum (in black), together with the simulated spectrum (in red). Very good simulation was obtained, and the hyperfine coupling constants values are typical for the imino-nitroxide radicals (a_{N1} = 9.08 G (nitroxyl); a_{N2} = 4.46 G (imino)).[8-10,20] No interaction between the two unpaired electrons was noticed, which can be due to the long distance between the two radical moieties.

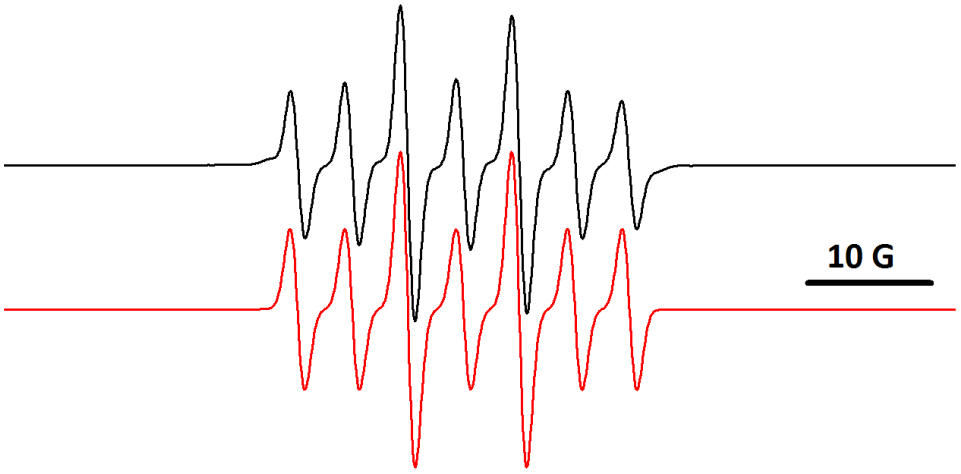

Figure 2. EPR spectrum of **7** in DCM (black) and simulation (red).

One of the most interesting properties of the stable betaine diradical **7** is its intense blue colour. The UV-Vis spectrum showed a maximum absorption at 552 nm (Figure 3), due to the extended conjugation system. Reduction of **7** with ascorbic acid or sodium ascorbate led to the corresponding hydrazine-hydroxylamine derivative, with a yellow colour, having a maximum absorption at 405 nm (Figure 3), and of course no EPR signals. This type of interconversion of such species is well known[21] and can be used to study or monitor redox reactions (by reduction the EPR signal disappears, but it is restored on oxidation).

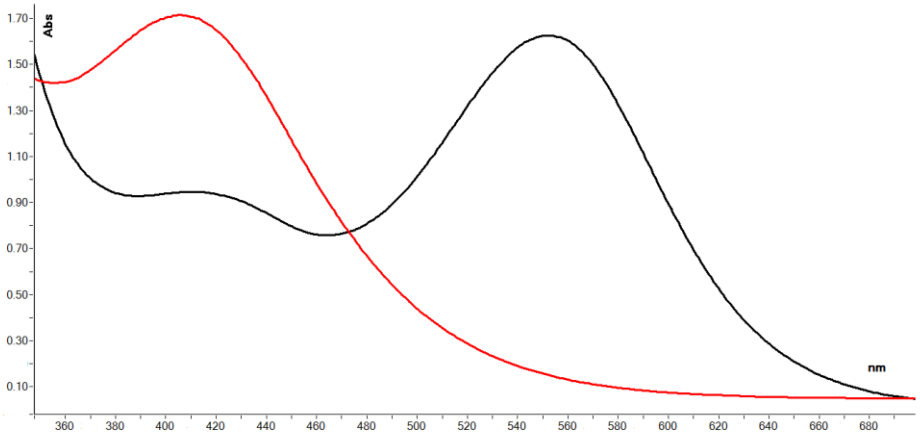

Figure 3. UV-Vis spectrum of compound **7** (black) and its reduced counterpart (red).

Conclusions

A stable betaine diradical with an intense blue colour and paramagnetic properties has been synthesized and characterized. By reduction, this is converted to the corresponding diamagnetic yellow derivative. The redox process is reversible and accompanied by a colour shift of about 150 nm.

Experimental Section

General. All chemicals and materials were purchased from Sigma-Aldrich, Alfa Aesar or Chimopar. 2,3-Bis(hydroxyamino)-2,3-dimethylbutane was synthesised following literature data.[18] NMR spectra were recorded in the appropriate deuterated solvents using a Varian Inova-400 spectrometer. IR spectra were recorded on a Bruker Vertex 70 spectrometer (as solid samples, ATR). UV-Vis spectra were recorded in methanol at ambient temperature on an UVD-3500 double beam spectrometer, using a quartz cell with 1 cm path length. EPR spectra were recorded in DCM, at room temperature, using a Jeol Jes-FA 100 spectrometer, with the

following typical settings: number of scans 1, centre field 3350 G, sweep field 100 G, frequency 9.42 GHz, power 1 mW, sweep time 60 s, time constant 0.1 s, modulation frequency 100 kHz, gain 100, and modulation width 1G.

Synthesis of the compounds 1-7

4-(*N′*,*N′*-Diphenylhydrazino)-3,5-dinitrobenzonitrile (1). 2.27 g (10 mmol) 4-chloro-3,5-dinitrobenzonitrile and 2.21 g (10 mmol) *N*,*N*-diphenylhydrazine hydrochloride were suspended in 100 mL ethanol, and 5 g of sodium hydrogen carbonate has been added under stirring. The mixture was refluxed for 2 h, filtered off, and the solid washed three times with 30 mL DCM. The solvent is removed under vacuum, affording the compound **1** a red solid. The yield is over 90% and the solid does not require further purification. IR (ATR, cm^{-1}): 3244, 3091, 2240, 1623, 1586, 1505, 1453, 1270, 1250, 1116, 764, 731, 532. ^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz): 9.99 (s, 1H, NH); 8.59 (s, 1H, H-3 or H-5); 7.85 (s, 1H, H-5 or H-3); 7.34 (dd, 4H, H-9-11-15-17, 7.3, 8.6); 7.10 (tt, 2H, H-10-16, 1.2, 7.3); 7.19 (dd, 4H, H-8-12-14-18, 1.2, 8.6). ^{13}C-NMR ($CDCl_3$, δ ppm): 146.05; 140.86; 134.55; 133.30; 129.52; 125.76; 120.44; 115.30; 100.84.

4-(Methoxyamino)-3,5-dinitrobenzonitrile (2). 2.27 g (10 mmol) 4-chloro-3,5-dinitrobenzonitrile and 1.25 g (15 mmol) methoxyamine hydrochloride were suspended in 70 mL ethanol, and 5 g of sodium hydrogen carbonate has been added under stirring. The mixture was refluxed for 2 h, filtered off, and the solid washed three times with 30 mL DCM. Few drops of concentrated hydrochloric acid are added, until the solution become yellow, and the solvent is removed under vacuum, affording the compound **2** as a yellow solid. Purification of the compound is acquired using silica gel column chromatography and DCM as eluent. The yield is about 70%. IR (ATR, cm^{-1}): 3239, 3113, 2943, 2235, 1627, 1533, 1278, 1055, 904, 643. ^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz): 10.29 (s, 1H, NH); 8.28 (s, 2H, CH-m); 3.81 (s, 3H, CH_3). ^{13}C-NMR ($CDCl_3$, δ ppm): 139.34; 136.69; 133.18; 115.23; 101.63; 64.21.

***N*-(4-Cyano-2,6-dinitrophenyl)-*N′*-phenyl-*N′*-[(phenyl-(4′-cyano-2′,6′-dinitrophenyl)]diazenium betaine (3).** 700 mg (2 mmol) compound **1** and 476 mg (2 mmol) compound **2** were dissolved in 250 mL DCM, and 20 g lead dioxide and 5 g anhydrous sodium sulfate was added. The mixture is well stirred for about 6 h, filtered off, the solid filtrate washed three times with 30 mL DCM, and the reunited solutions evaporated under vacuum. Purification of the compound is achieved using silica gel column chromatography and DCM as eluent, affording an intense blue-black solid. The yield is about 65%. IR (ATR, cm^{-1}): 3074, 2233, 1531, 1423, 1368, 1345, 1214, 1166, 906, 778, 714, 577. ^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz): 8.03 (s, 2H, CH-m); 7.43 (d, 2H-8-12, 7.3); 7.48 (t, 2H-9-11, 7.3); 7.57 (t, 1H, H-10, 7.3); 6.83 (dd, 1H, H-14, 2.5, 10); 6.58 (dd, 1H, H-15, 1.7, 10); 6.84 (dd, 1H, H-17, 1.7, 9.9); 7.92 (dd, 1H, H-18, 1.7, 9.9); 8.46 (s, 2H, H-21,23). ^{13}C-NMR (acetone-d_6, δ ppm): 162.70; 144.23; 144.17; 142.95; 142.63; 142.24; 140.36; 133.96; 133.71; 133.44; 131.43; 130.08; 129.20; 129.09; 128.25; 127.38; 107.64; 105.41.

3,5-Dinitro-4-[*N′*-phenyl-*N′*-[*p*-(4′-cyano-2′,6′-dinitrophenyl)phenylamino]hydrazino]-benzonitrile (4). Reduction of compound **3** to **4** was achieved using a biphasic liquid-liquid system, DCM-water; thus, compound **3** dissolved in DCM is stirred with an aqueous solution

containing ascorbic acid in excess, until the initial blue solution become yellow. The yield is practically quantitative. IR (ATR, cm^{-1}): 3293, 3085, 2235, 1623, 1537, 1502, 1354, 1271, 1012, 730, 583. ^{1}H-NMR (DMSO-d_6, δ ppm, *J* Hz): 10.78 (s, 1H, NH); 9.94 (s, 1H, NH); 8.75 (s, 2H, CH-m); 8.60 (s, 2H, CH-m); 7-7.4 (m, 4H). ^{13}C-NMR (DMSO-d_6, δ ppm); 145.55; 142.33; 140.15; 138.68; 136.61; 135.95; 135.25; 133.83; 128.79; 124.16; 121.46; 120.92; 119.29; 116.32; 116.15, 99.34; 98.92.

3,5-Dinitro-4-[*N′*-phenyl-*N′*-[*p*-(4′-formyl-2′,6′-dinitrophenyl)phenylamino]hydrazino]-benzaldehyde (5). 580 mg (1 mmol) compound **4** is dissolved in 500 ml DCM, cooled to -78 ºC in a dry ice –acetone bath, and 2.2 mL of DIBAL-H solution (1 M) is added under stirring. The reaction mixture is kept at the same temperature for 1 h, and then let to reach room temperature. Afterwards, 200 mL aqueous hydrochloric acid (1 M) is added, the biphasic system stirred, and the organic phase separated, dried over anhydrous sodium sulfate and solvent removed under vacuum. The residue is chromatographed on a silica gel column using DCM as eluent, affording a yellow solid. The yield is about 35%. IR (ATR, cm^{-1}): 3289, 3067, 2957, 2924, 2854, 1695, 1616, 1534, 1507, 1263, 1216, 1108, 698. ^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz): 10.09(s, 1H, NH); 9.99(s, 1H, NH); 9.88 (s, 1H, CHO); 9.84 (s, 1H, CHO); 8.64 (s, 4H, H-3, H-5 and H-21, H-23); 7.31 (dd, 2H, H-9, H-11, 7.6, 8.2); 7.22 (t, 1H, H-10, 7.6); 7.13 (d, H-8, H-12, 8.2); 7.08(d, 2H, H-15, H-17, 8.8); 7.00(d, 2H, H-14, H-18, 8.8). ^{13}C-NMR ($CDCl_3$, δ ppm): 186.67; 186.58; 145.67; 144.83; 141.62; 140.87; 139.00; 138.82; 132.40; 134.26; 129.97; 126.85; 122.17; 119.98; 122.08. Elemental analysis: $C_{26}H_{17}N_7O_{10}$; found (%): C 53.07; H 2.95; N 16.55; calculated C 53.16; H 2.92; N 16.69.

***N*^{1}-Phenyl-*N*^{4}-[4-(1-oxyl-4,5-dihydro-1*H*-imidazol-2-yl)-2,6-dinitrophenyl]-1,4-benzenediimine *N*^{1}-[4-(1-oxyl-4,5-dihydro-1*H*-imidazol-2-yl)-2,6-dinitrophenyl]imine diradical (7).** To 60 mg (0.1 mmol) compound **5** dissolved in 100 mL mixture of DCM-methanol (1/1 v/v) was added 200 mg of bis(hydroxyamino)-2,3-dimethylbutane, and the mixture left 3 days to react. The solution is filtered off, the solvent removed and the residue (bis-imidazolidinediol **6**) is re-dissolved in DCM. 1 g lead dioxide and 1 g of anhydrous sodium sulfate is added, and the mixture stirred for 1 h, filtered off, and the solvent removed under vacuum. The residue is chromatographed on silica gel using DCM as eluent, affording a blue-black solid. The yield is about 25%. IR (ATR, cm^{-1}): 3123, 3067, 2985, 2927, 2877, 1623, 1587, 1535, 1507, 1363, 1211, 1089, 703. Elemental analysis: $C_{38}H_{37}N_{11}O_{10}$; found (%): C 56.37; H 4.51; N 18.97; calculated C 56.5; H 4.62; N 19.07.

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