

*Dedicated to Professor Vasile Pârvulescu
on the occasion of his 70th anniversary*

ALKYLATION OF MORPHOLINE WITH 2-(CHLOROMETHYL)-NITRONYL-NITROXIDE: A NEW LIGAND AND ITS NICKEL COMPLEX

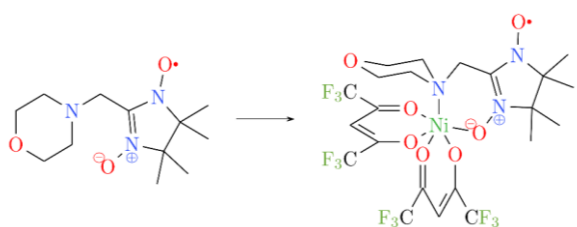
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A new nitronyl nitroxide ligand (**L**) has been obtained by the alkylation reaction of morpholine with 2-(chloromethyl)-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazolyl-1-oxyl 3-oxide (**NIT-CH₂Cl**). The reaction of **L** with [Ni(hfac)₂(H₂O)₂] in hot *n*-heptane affords the mononuclear complex, [NiL(hfac)₂] (**1**), characterized herein by single crystal X-ray diffraction, FTIR and UV-Vis spectroscopies. Within the nickel(II) complex, **L** acts as a chelating ligand, through one aminoxyl oxygen and through the morpholine nitrogen atom. The crystal structure of alkylation agent (**NIT-CH₂Cl**) has been solved.

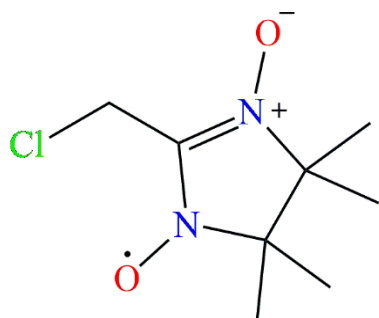


INTRODUCTION

The nitronyl nitroxide radical synthesized from chloroacetaldehyde (2-(chloromethyl)-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazolyl-1-oxyl 3-oxide, **NIT-CH₂Cl**) is among the first radicals reported by Ullman in 1972 – Scheme 1.¹ This compound, along with its bromine equivalent were successfully used as alkylating agents of various substrates. Hence compound **NIT-CH₂Cl** has been used for amino acids^{2,3} and macrocycles^{4,5} spin labeling, for free radical scavenger properties,⁶ as well as for functionalization of dendrimers.⁷ The alkylation products were further used in molecular

magnetism,^{8–10} or as dual fluorescent and magnetic probes.¹¹ Although the majority of examples represents N-alkylations, O-alkylations have been reported as well.^{5,12} We recall here a representative example, namely the diradical obtained by the alkylation of piperazine used as polychelating ligand to form a Ni(II) dinuclear complex.⁸ Morpholine could generate a monoradical prone to act as chelating ligand. In this paper we report on a new nitronyl nitroxide ligand, **L**, which is obtained by the alkylation of morpholine with **NIT-CH₂Cl**. The ligand, **L**, has been reacted with [Ni(hfac)₂(H₂O)₂] to obtain a mononuclear complex.

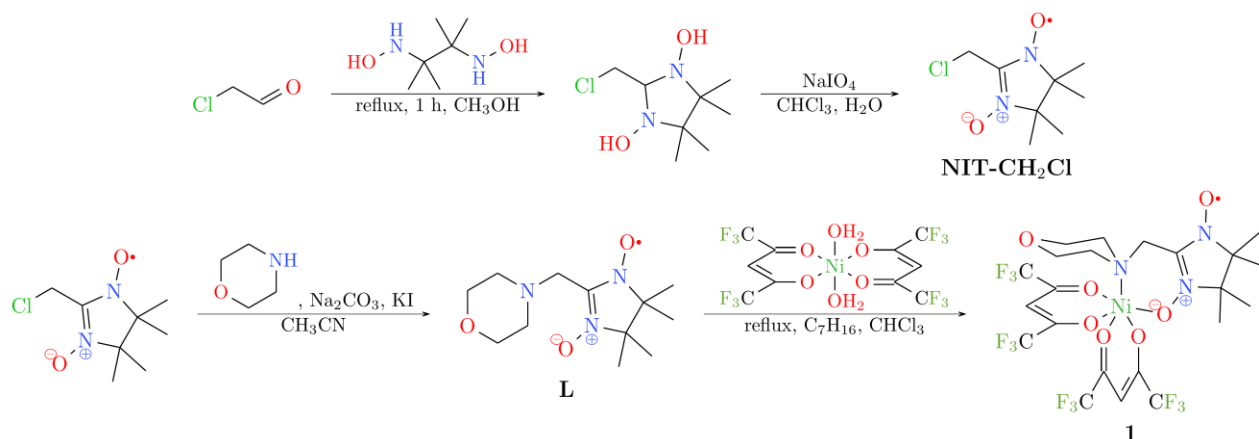
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Scheme 1 – Structure of ligand **NIT-CH₂Cl** (*i.e.* 2-(chloromethyl)-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazolyl-1-oxyl 3-oxide).

RESULTS AND DISCUSSION

The attachment of the radical moiety of **NIT-CH₂Cl** to the morpholine is accomplished by



Scheme 2 – Synthesis protocols for **NIT-CH₂Cl**, **L** and **1**.

Description of the crystal structures

Compound **NIT-CH₂Cl** crystallizes in the monoclinic crystal system, *P*2₁/*n* space group (Table 1). The asymmetric unit contains

two radical molecules. The distances between the heteroatoms within the radical moiety are N1-O1 = 1.268(4), N2-O2 = 1.277(4), N3-O3 = 1.280(5), and N4-O4 = 1.278(5) Å.

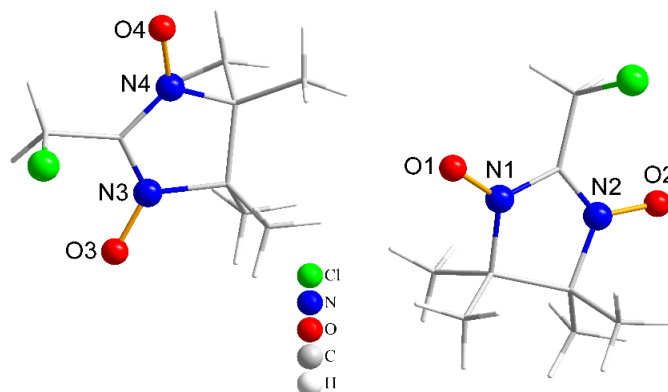


Fig. 1 – Perspective view of the asymmetric unit of **NIT-CH₂Cl** determined by X-ray diffraction.

Compound **1** crystallizes in the triclinic crystal system, *P*-1 space group (see Table 1). In the mononuclear nickel(II) complex, the radical **L** acts as a chelating ligand (Fig. 2). The nickel ion shows a coordination number of 6, with a slightly distorted octahedral stereochemistry (SHAPE analysis: $O_h = 0.211$). The coordination sphere is made by 5

oxygen atoms arising from two chelating hfac⁻ ligands and one aminoxyl oxygen, and one aminic nitrogen, with distances varying between 2.021(2) and 2.171(2) Å, the longest one corresponding to the Ni-N bond. The distances between the heteroatoms within the radical moiety are N1-O1 = 1.292(3) and N2-O2 = 1.273(3) Å (Table 2).

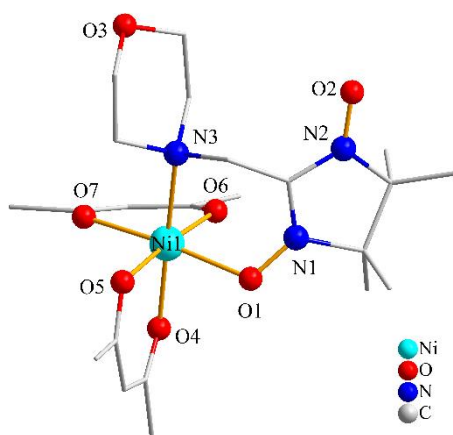


Fig. 2 – Crystal structure of **1**. Hydrogen and fluorine atoms have been omitted for clarity.

One of the CF₃ groups from each hfac⁻ ligand presents crystallographic disorder, the three fluorine atoms occupying 6 positions with 0.5 occupancy (Fig. 3). As we and others previously observed in the case of hfac⁻ anion,^{13,14} the fluorine atoms from neighboring CF₃ groups establish F...F short

contacts.^{15–17} In the present case the packing diagram of **1** shows that two out of three F atoms from a CF₃ group exhibit short distances with two other F atoms from two neighboring molecules, with F...F distances in the range 2.73–2.80 Å, and angles ranging from 114 to 138° (Fig. 3 and Table 3).

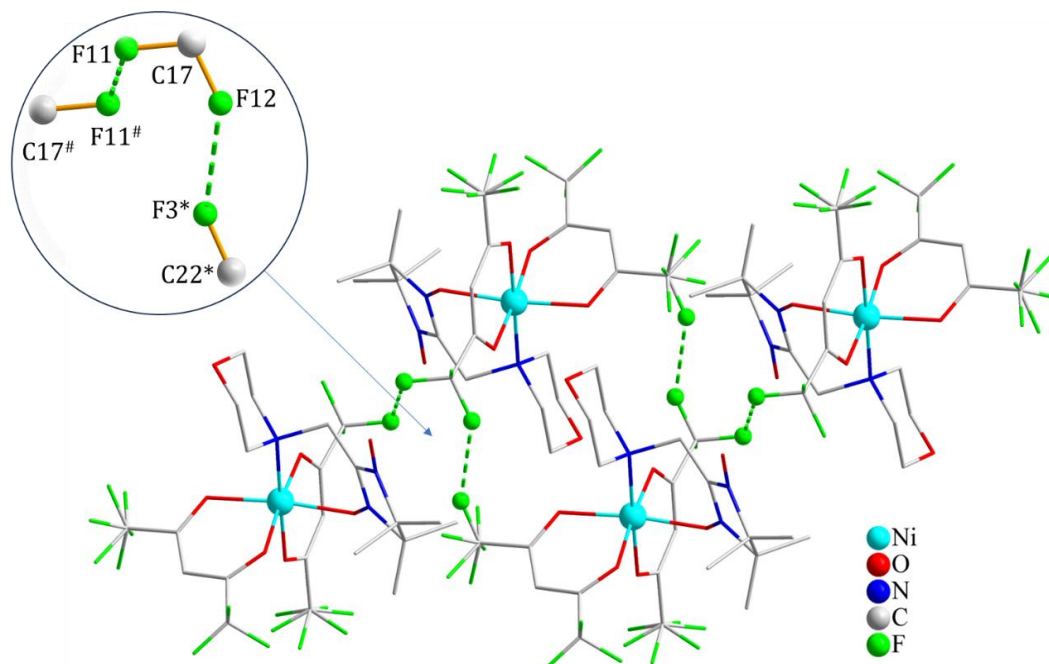


Fig. 3 – Perspective view of the F...F interactions between four neighboring molecules of compound **1** representing a sequence from a supramolecular chain. Insets present the corresponding distances and angles. Hydrogen atoms have been omitted for clarity.

Symmetry operations: * = 1-x, 1-y, 1-z; # = -x, 1-y, 1-z.

The electronic spectra (Fig. 4) of the alkylating agent (**NIT-CH₂Cl**) and the complex **1**, were recorded in the solid state, using the diffuse reflectance technique. The UV-Vis spectrum of compound **1** shows, apart from the bands arising

from the organic ligands, two other bands which are due to the d–d transitions of the hexacoordinated Ni(II) ion ([NiII(O₄O'N)] chromophore): ${}^3A_2 \rightarrow {}^3T_2$ (1092 nm) and ${}^3A_2 \rightarrow {}^3T_1$ (767 nm), assuming the O point group.

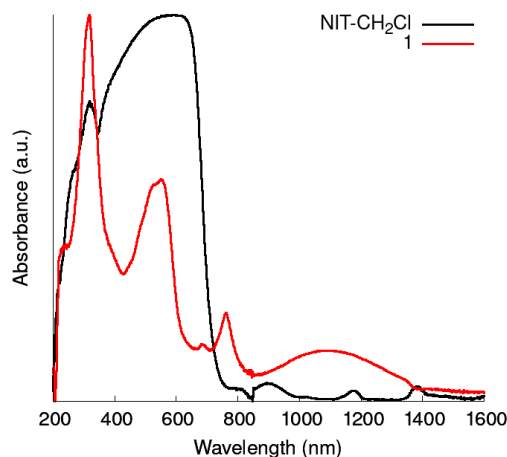


Fig. 4 – Electronic spectra for **NIT-CH₂Cl** and **1**.

Table 1

Crystallographic data and structures refinement for compounds **NIT-CH₂Cl** and **1**

Compound	NIT-CH₂Cl	1
Chemical formula	C ₁₆ H ₂₈ N ₄ O ₄ Cl ₂	C ₂₂ H ₂₄ N ₃ O ₇ F ₁₂ Ni
M (g mol ⁻¹)	411.32	729.15
Temperature, (K)	293(2)	293(2)
Wavelength, (Å)	0.71073	0.71073
Crystal system	<i>Monoclinic</i>	<i>Triclinic</i>
Space group	<i>P21/n</i>	<i>P-1</i>
<i>a</i> (Å)	18.5693(17)	9.6391(3)
<i>b</i> (Å)	6.3805(4)	11.5155(3)
<i>c</i> (Å)	18.7096(18)	14.4953(4)
α (°)	90	90.133(2)
β (°)	113.398(11)	95.879(3)
γ (°)	90	109.040(3)
V (Å ³)	2034.5(3)	1511.85(8)
Z	4	2
<i>D_c</i> (g cm ⁻³)	1.343	1.602
μ (mm ⁻¹)	0.347	0.720
<i>F</i> (000)	872	738
GOF	0.996	1.043
Final <i>R</i> ₁ , w <i>R</i> ₂ [<i>I</i> >2σ(<i>I</i>)]	0.0765, 0.2316	0.0541, 0.1541
<i>R</i> ₁ , w <i>R</i> ₂ (all data)	0.1160, 0.2811	0.0820, 0.1718
Δρ _{min} /Δρ _{max} (e Å ⁻³)	0.53, -0.41	0.62, -0.30

Table 2
Selected bond distances [Å] and angles (°) for compound **1**

Bond distances [Å]		Angles (°)	
Ni1-O1	2.051(2)	O1-Ni1-O4	85.91(9)
Ni1-O4	2.037(2)	O1-Ni1-O5	87.47(8)
Ni1-O5	2.024(2)	O1-Ni1-O6	88.92(9)
Ni1-O6	2.021(2)	O1-Ni1-O7	173.28(8)
Ni1-O7	2.045(2)	O1-Ni1-N3	93.28(8)
Ni1-N3	2.171(2)	O4-Ni1-O5	89.34(9)
N1-O1	1.292(3)	O4-Ni1-O6	87.48(9)
N2-O2	1.273(3)	O4-Ni1-O7	87.55(9)
		O4-Ni1-N3	179.16(8)
		O5-Ni1-O6	175.34(8)
		O5-Ni1-O7	94.02(8)
		O5-Ni1-N3	90.41(7)
		O6-Ni1-O7	89.24(8)
		O6-Ni1-N3	92.72(8)
		O7-Ni1-N3	93.27(7)

Table 3
Selected distances [Å] and angles (°) for the F...F interactions within compound **1**

F...F distances	[Å]
F3...F12*	2.80
F11...F11#	2.73
Angles	(°)
C17-F11-F11#	114.0
C17-F22-F3*	137.5
C22*-F3*-F12	138.3

Symmetry operations: * = 1-x, 1-y, 1-z; # = -x, 1-y, 1-z

EXPERIMENTAL

All starting materials were of reagent grade and used without purification. All manipulations were performed under aerobic conditions. Synthesis of 2,3-dimethyl-2,3-dinitrobutane¹⁸ and 2,3-bis(hydroxylamino)-2,3-dimethylbutane¹⁹ were performed following the reported procedures. Compound **NIT-CH₂Cl** has been obtained following the general procedure for synthesizing the nitronyl nitroxides.^{1,20-22}

Synthesis of **NIT-CH₂Cl**

To a solution of 2,3-bis(hydroxylamino)-2,3-dimethylbutane (0.1000 g, 0.6747 mmol) in 20 mL MeOH, chloroacetaldehyde 55 wt. % aqueous solution (77.9 µL, 0.6747 mmol) was added. The mixture was refluxed for 1 h and then the solvent was evaporated under vacuum. The yellow intermediate was dissolved in 15 mL CHCl₃ and the solution was cooled on ice bath. Further, NaIO₄ (0.1443 g, 0.6747 mmol) was added under vigorous stirring, followed by 5 mL of water. The biphasic system was thoroughly stirred at 0 °C for 15 min. The organic phase was isolated using a separatory funnel and dried over MgSO₄. The solvent was evaporated under vacuum, resulting in the crude violet

product, which was purified using column chromatography with diethyl ether. Yield: 46%. Selected FTIR ATR peaks (cm⁻¹): 3443w, 2988w, 2943w, 1450vs, 1431vs, 1375vs, 1256w, 1211s, 1140m, 901w, 718w, 635w, 542w, 455w. UV-Vis bands (nm): 320, 500–650, 897, 1175, 1383, 1701. ¹H-NMR (500 MHz, DMSO-*d*₆, δ ppm, J Hz): 4.37 (s, 2H, CH₂), 1.12 (s, 12H, CH₃) ppm. ¹³C-NMR (125 MHz, DMSO-*d*₆, δ ppm): 143.3, 64.8, 31.8, 19.1 ppm. N.B. **NIT-CH₂Cl** has been reduced in the test tube with phenylhydrazine prior to the analysis. The signals corresponding to phenylhydrazine were subtracted and neglected. MS (+ESI): [M+H] = 206.0 (*m/z*) (exact mass 205.07 Da) in diisopropyl ether. Crystals of **NIT-CH₂Cl** suitable for single crystal X-ray diffraction measurements were obtained from a solution of the radical in diisopropyl ether using rotary evaporator.

Synthesis of **L**

A suspension of morpholine (0.0212 g, 0.2431 mmol), **NIT-CH₂Cl** (0.0500 g, 0.2431 mmol), Na₂CO₃ (0.0258 g, 0.2431 mmol), and KI (0.0040 g, 0.0243 mmol) in acetonitrile (10 mL) was stirred at room temperature for 30 min and then stirred at 60 °C for other 75 minutes. After cooling the pink-violet solution to room temperature, water was added (10 mL) and the product was extracted with chloroform. The organic

phase was dried over MgSO₄ and the solvent was evaporated under vacuum. Purification was realized by column chromatography (SiO₂), starting with diethyl ether as eluent and continuing with chloroform and methanol gradient up to 10%. Yield: 42%. Selected FTIR ATR peaks (cm⁻¹): 3222–3600br, 2979vs, 2931vs, 2862vs, 2822s, 2500–2700br, 2469m, 1658m, 1442vs, 1415vs, 1369vs, 1325vs, 1263s, 1218s, 1182vs, 1068m, 999m, 603. MS (+ESI): [M+H]⁺ = 257.1 (m/z) (exact mass 256.17 Da) in dichloromethane.

Synthesis of [NiL(hfac)₂] (1)

A solution of **L** (0.0080 g, 0.0312 mmol) in chloroform (5 mL) was added to a boiling solution of nickel hexafluoroacetylacetonate dihydrate (0.0156 g, 0.0312 mmol) in *n*-heptane (10 mL). The resulting pink solution was stirred for one minute and then cooled to room temperature. Pink crystals were formed upon evaporation of the solvent at room temperature. Yield: 22%. Selected FTIR ATR peaks (cm⁻¹): 2962s, 2908m, 1645m, 1488m, 1446m, 1409w, 1340w, 1296s, 1200m, 1084vs, 1016vs, 790vs, 672m, 561m. UV-Vis bands (nm): 318, 554, 767, 1092.

X-ray data collection and crystal structure refinement

X-ray diffraction measurements were performed on a Rigaku XtaLAB Synergy-S diffractometer operating with Mo-K α ($\lambda = 0.71073$ Å) micro-focus sealed X-ray tube. The crystal was kept at 293(2) K during data collection. Using Olex2,²³ the structure was solved with the SHELXS²⁴ structure solution program using Direct Methods and refined with the SHELXL²⁵ refinement package using Least Squares minimization. The non-H atoms were refined with anisotropic displacement parameters. A summary of the crystallographic data and the structure refinement are given in Table 1. Deposition numbers for **NIT-CH₂Cl** (2319944) and **1** (2332913) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

Physical measurements

UV-Vis spectra were recorded on a JASCO V-670 spectrophotometer equipped with diffuse reflectance accessories, on MgO diluted samples from 200 to 1600 nm. IR spectra were recorded on a FTIR Bruker Tensor V-37 spectrophotometer (KBr pellets) in the range of 4000–400 cm⁻¹ for **NIT-CH₂Cl**, and on a FTIR Bruker Vertex 70 spectrometer in the 4500–400 cm⁻¹ range using the ATR technique for **L** and **1**.

For MS spectra Varian 310 – MS LC/MS/MS triple quadrupole mass spectrometer fitted with an electrospray ionization interface (ESI) was used. Air was used as drying gas at a pressure of 19 psi and temperature depending on the experiment. The nebulizing gas was nitrogen to 40 psi and the needle voltage had been established to the potential +5000 V for positive ionization. Thus, protonated molecular ion obtained was selected by the first quadrupole. Into the second quadrupole, the protonated molecular ion was fragmented by

collision with an inert gas (Ar) to 1.5 mTorr pressure. Fragments were analyzed by the third quadrupole. Prior to these experiments it was performed the tuning of mass spectrometer using PPG both for positive and negative.

NMR spectra were recorded on Bruker Avance III UltraShield Plus 500 MHz spectrometer, operating at 11.74 T, corresponding to the resonance frequency of 500.13 MHz for the ¹H nucleus. Chemical shifts (δ) are referenced to residual peaks of solvent (DMSO-*d*₆) and are reported in parts per million (ppm).

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