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► **To cite this version:**

Jean-Pierre Costes. A simple reaction pathway allowing easy EPR characterization of N-oxyl radicals. New Journal of Chemistry, 2024, 48 (18), pp.8034-8037. 10.1039/d4nj00943f . hal-04575708

HAL Id: hal-04575708

<https://hal.science/hal-04575708v1>

Submitted on 15 May 2024

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A simple reaction pathway allowing easy EPR characterization of N-oxyl radicals†

Jean-Pierre Costes 

Mixing a dinuclear Cu^{II} complex with an excess of primary or secondary amine in the presence of dioxygen with or without toluene yields N-oxyl radicals and Cu^I entities. The EPR spectra of these radicals clearly show their evolution from the initial to the final state. Under these mild conditions, it is not possible to obtain Tempo radicals, steric crowding impeding the approach of the corresponding amine into the Cu^{II} coordination sphere.

In the past, various oxidative methods of aliphatic, cyclic or aromatic amines, with the use of *t*-butyl hydroperoxide,¹ hydrogen peroxide and phosphotungstic acid,² and photochemical generation by ultraviolet light,³ have allowed the formation of N-oxyl radicals. Some years ago we published the structure of a dinuclear Cu^{II} complex in which the two copper ions are linked by a dideprotonated tetraacethylethanato ligand (Tae), while *N,N,N',N'*-tetramethylethylenediamine (tmen) completes the coordination sphere of each copper ion (Fig. 1).⁴ Although the structural determination shows that the Cu^{II} ions are not equivalent, the equatorial Cu–O and Cu–N bond lengths of each copper ion are similar, thus confirming the presence of two Cu^{II} ions in the solid state. The magnetic susceptibility measurements indicate that the $\chi_M T$ value of the dinuclear unit in the solid state at room temperature is equal to 0.8 cm³ mol⁻¹ K, in agreement with the presence of two Cu^{II} ions. The EPR spectrum at room temperature in dichloromethane displays a seven-line pattern (Fig. S1, ESI†), with the two unpaired electrons exchanging quickly on the EPR time scale between the two sites. This is possible as the exchange parameter *J* (0.08 cm⁻¹) was found to be one order of magnitude larger than the isotropic value of the hyperfine constant (0.009 cm⁻¹). As a mixed-valence Cu^{II}–Cu^I complex could also give a seven-line pattern,⁵ the Evans' method⁶

yielded a 2.5 μ B magnetic moment, in agreement with two Cu^{II} ions for the dissolved dinuclear complex.⁴

It was also remarked that the isotropic A_{Cu} coupling constant was solvent dependent, varying from 48 G in dichloromethane to 38 G in isopropyl amine. Such an A_{Cu} decrease is consistent with a change in the copper coordination sphere,⁷ and confirms that the amine nitrogen atom coordinates to the two copper ions in the axial position. Surprisingly, supplementary changes were observed in the room temperature EPR spectrum, with a time dependent intensity decrease of the copper signal and the appearance of a new signal centered at $g = 2.006$. This signal consists of three main lines separated by 15 G coming from hyperfine interaction with a nitrogen nucleus, typical of N-oxyl radicals (Fig. 2). Each line is further split into three lines due to hyperfine coupling with neighboring hydrogen nuclei. This spectrum corresponds to the isopropyl N-oxyl radical (CH₃)₂CHNHO, first described in the literature in 1965 as a mixture of two radicals, considered as an unstable radical having two A values ($A_N = 15$ and $A_H = 5$ G). A simulation of the above signal yields an A_N value of 15.2 G and two A_H values equal to 5 and 4 G, in good agreement with the previous literature data (Fig. S2, ESI†).

In view of this result, we tried to use piperidine as a starting nitrogen ligand. A mixture of the dinuclear Cu^{II} complex with an excess of piperidine in toluene as a solvent yielded a quick

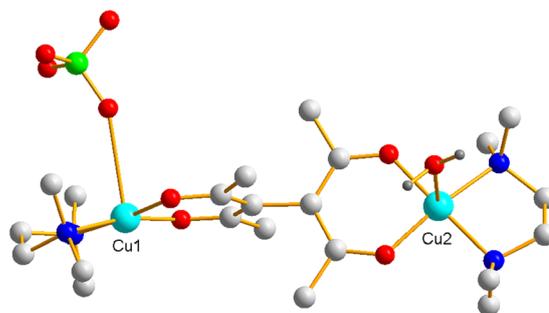


Fig. 1 Diamond plot of the dinuclear complex used in this work.

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† Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d4nj00943f>

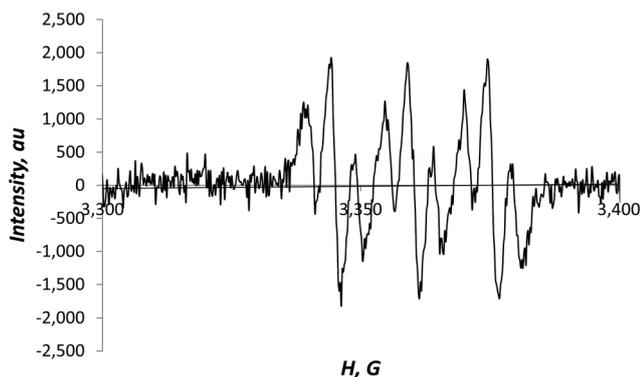


Fig. 2 EPR solution spectrum of the isopropyl nitroxide radical ($\text{CH}_3)_2\text{CHNO}$ in pure isopropyl amine at room temperature.

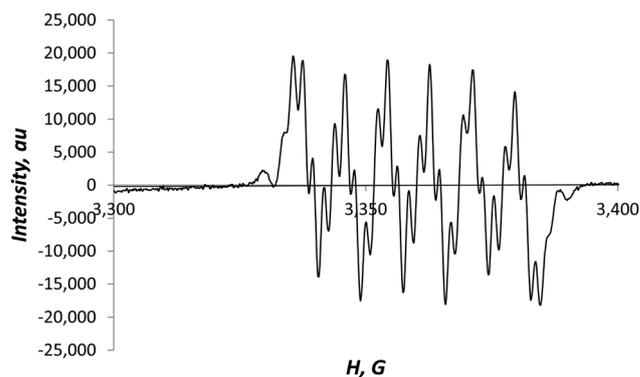


Fig. 4 EPR solution spectrum of the 4-methylpiperidine nitroxide radical 4-MepipNO in pure 4-methylpiperidine at room temperature.

bleaching of the solution corresponding to a decrease of the EPR signal coming from the copper complex, along with the appearance of a novel signal centered at $g = 2.006$ presenting 11 lines (Fig. 3). An expansion of that signal is shown in Fig. 5.

The piperidine N-oxyl radical pipNO \cdot was first described in 1965 with a lifetime of a few minutes.² But a different preparation pathway allowed a complete EPR study in 1969.³ It was reported that its EPR spectrum results from hyperfine coupling to the nitrogen atom and to the four hydrogen atoms bonded to the carbon atoms adjacent to the nitrogen atom, with the nitrogen hyperfine coupling independent of temperature contrary to the hydrogen hyperfine coupling. This temperature dependence is due to the existence of two chair conformations, which undergo interconversion, the two conformers being identical. A rapid interconversion coming from ring inversion averaging the coupling of axial and equatorial H is observed at 110 °C and 13 over the 15 expected lines are seen. In our spectrum taken at lower temperature (room temperature), the presence of a lower interconversion rate broadens the spectrum and we only see 11 broad lines, among the 15 expected lines.

Replacement of piperidine by furnishes a new spectrum containing six main lines showing supplementary hydrogen coupling constants (Fig. 4). Introduction of a 4-methyl substituent in the piperidine cycle gives two different conformers. In the present example, the two conformers are different and the

axial and equatorial positions cannot be interconverted and several thin lines, coming from the hyperfine hydrogen coupling of 3 G, are observed. On the contrary, with the use of 2,2,6,6-tetramethylpiperidine, it is not possible to obtain the EPR signal of the Tempo radical. In that particular case, the steric hindrance coming from the four methyl groups of 2,2,6,6-tetramethylpiperidine and the crowded copper coordination spheres of the dinuclear Cu^{II} complex (presence of tmen with its four methyl groups and of the Tae ligand, perpendicular to the mean tmen plane) must impede an axial approach of this particular amine.

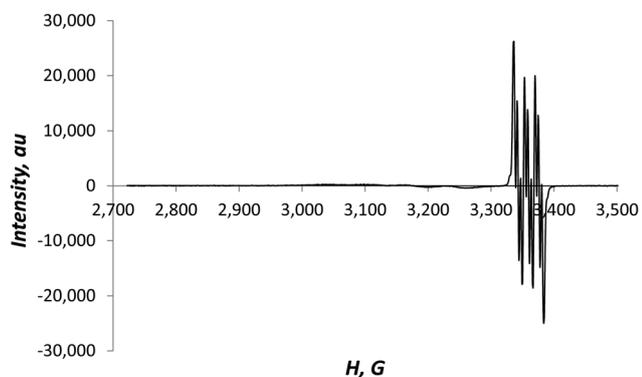


Fig. 3 EPR spectrum of the copper complex with piperidine in toluene at room temperature, with a 1/1000 complex/piperidine molar ratio.

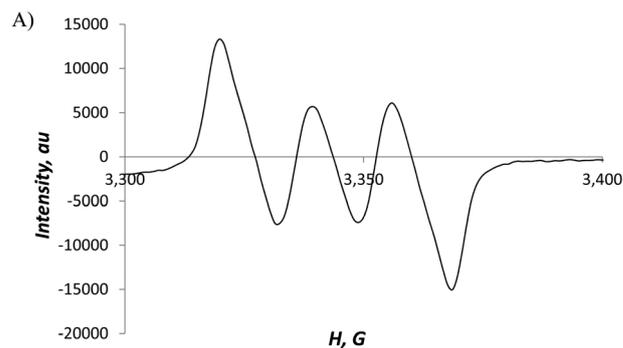
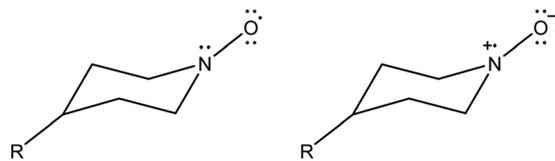


Fig. 5 Expanded radical spectra in pure piperidine at room temperature: (A) 15 minutes after mixing; (B) one hour later.

In order to see the decrease of the Cu^{II} signal and the increase of the radical signal, EPR spectra were taken 15 minutes after dissolution of the dinuclear copper complex into pure piperidine and one hour later (Fig. S4, ESI† and Fig. 5).

A supplementary remark can be made in viewing the expanded spectra of the radical species (Fig. 5). The radical spectrum consists first of a wide three band spectrum coming from the hyperfine coupling of the free electron with the nitrogen nuclear spin, while the hyperfine coupling with the hydrogen nuclear spins appears later. This phenomenon could result from a concentration problem, as observed in the solution spectra of the Tempo radicals. A look at the corresponding *g* values indicates that we observe a slight shift of the *g* value, from 2.0156 for the large signal to 2.0056 for the final spectrum. If the last value corresponds to the expected value for an N-oxyl radical, the wide three-line signal centered at *g* = 2.0156 is more puzzling. In order to check this point, the dinuclear complex was dissolved in piperidine and the EPR tube was frozen to 90 K (Fig. S5, ESI†). Then, the temperature was slowly increased and different spectra were run in two hours' time. At 90 K the radical signal corresponds to two large lines, while the three-line signal begins to appear at 250 K. Going from 250 K to 260 K, a shift of the radical *g* value is clearly observed and, from 260 to 290 K, the *g* value remains constant while the intensity of the lines due to the hyperfine hydrogen coupling increases. To come back to the weak shift of the *g* value, which is only observed below 260 K, we must remember that the radical formation occurs in the Cu^{II} coordination sphere (decrease of the *A*_{Cu} parameter), so that the radicals that appear at the beginning of the reaction are in close vicinity of the remaining Cu^{II} ions, what could explain the signal width. Then their dilution in the solution, favored by the temperature increase and time, could be responsible of the observed slight shift. Such an observation does confirm the presence of a unique radical species. Furthermore, the EPR spectrum corresponding to a solution of the dinuclear complex in pure 4-methylpiperidine at room temperature (Fig. S6, ESI†), registered a few minutes after mixing and at room temperature, gives again a three line spectrum centered at the expected *g* value for the N-oxyl radical (2.006). This observation seems surprising at first view if we remember that the final spectra corresponding to these two radicals are quite different. In a recent publication,⁸ Gerard Parkin described a convenient approach for the construction of Lewis structures. The author specified that his approach can also be used for radicals, indicating that in such a case the octet configuration cannot be achieved for the entire set of atoms. In the retained Lewis structure for the N-oxyl radicals (Scheme 1, left), we can see that the nitrogen atom has an octet configuration while a septet configuration is present for the oxygen atom. Such a structure does agree with the observation of an identical triplet spectrum at the first stage of the reaction with piperidine or 4-methylpiperidine. But it is possible to imagine a second Lewis structure with a dative N–O bond, in which the free electron is then located on the nitrogen atom. In this later Lewis structure, the oxygen atom presents an octet configuration and the



Scheme 1 Lewis structure evolution of the N-oxyl radicals: R = H, pipNO•; R = CH₃, 4-MepipNO•.

nitrogen atom a septet configuration (Scheme 1, right). This migration of the free electron does agree with the evolution of the EPR signals, the interaction with the nuclear spins of the hydrogen atoms yielding different spectra for the radicals derived from piperidine or 4-methyl piperidine. Note that this migration disadvantages the dimerization of these radicals.

Although [(tmen)Cu(Acac)H₂O]X complexes were known for a long time and used as suitable solvatochromic indicators,^{9,10} the structural determination of the complex with X = PF₆⁻ was reported in 2008 only.¹¹ The main difference between this mononuclear complex and our dinuclear copper complex comes from the axial Cu–O involving the coordinated water molecule, which varies from 2.377(2) to 2.496(3) Å, respectively. This bond length change comes from the presence of six surrounding methyl groups (four from the tmen ligand and two from the Tae ligand) around the copper ion in the dinuclear complex instead of four (from the tmen ligand only) for the mononuclear copper complex. In piperidine as a solvent, the water molecule of [(tmen)Cu(Acac)H₂O]ClO₄ is replaced by piperidine, which is clearly shown by the decrease of the isotropic *A*_{Cu} coupling constant, from 80 to 60 G (Fig. S7, ESI†).⁷ And the same radical spectrum does appear. We can note that our dinuclear Cu complex seems to be more efficient in the formation of radicals, with a complete disappearance of the EPR signals coming from the dinuclear complex (Fig. 3), while the EPR signal of the mononuclear Cu complex decreases but remains always present along with the radical. Eventually nothing happens after mixing of the mononuclear Cu^{II} complex with 2,2,6,6-tetramethylpiperidine. The *A*_{Cu} hyperfine coupling constant remains equal to 80 G and there is no formation of the expected Tempo radical, thus confirming that the steric hindrance of 2,2,6,6-tetramethylpiperidine and of the Cu^{II} complex (presence of tmen around the copper coordination sphere) impedes an axial approach of the amine. This supplementary observation does confirm that the reaction takes place in the coordination sphere of the Cu^{II} ions.

From these preliminary results, it is clear that we cannot completely explain what happens but we can highlight some interesting experimental observations. First, we must recall that these experiments are realized in the presence of Cu^{II} complexes, an excess of primary or secondary amine and dioxygen. Then, dissolution of these copper complexes in a solvent such as toluene, or dichloromethane, in the presence of a primary or secondary amine or even in a pure amine, yields N-oxyl radicals, whatever the nuclearity of the copper complex. Important information comes from the fact that an axial amine coordination to a Cu^{II} centre is needed for the appearance of the

corresponding N-oxyl radical, as indicated by the decrease of the hyperfine A_{Cu} parameter. On the contrary, a sterically hindered amine such as 2,2,6,6-tetramethylpiperidine cannot be coordinated to the Cu^{II} centre and the reaction does not occur. When piperidine is coordinated to the Cu^{II} ion in an equatorial position with a shorter Cu–N bond (2.020(6) Å), the formation of an N-oxyl radical is again not observed.¹² It appears that an axial coordination of the nitrogen atom with a bond around 2.3–2.4 Å is needed to induce the formation of N-oxyl radicals. But we know nothing about the possible role of the water molecule present in the two complexes, the presence of an excess of amine or the way the dioxygen reacts to yield N-O_2^- species able to reduce Cu^{II} ions to Cu^{I} ions and give N-oxyl radicals. Although the reaction mechanism remains to be confirmed, this communication evidences an easy preparation of N-oxyl radicals under mild conditions with the use of a dinuclear Cu^{II} complex in the presence of an excess of primary or secondary amine and of dioxygen, thus allowing a clean EPR characterization of known or original N-oxyl radicals.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

The author is grateful to people from the Laboratoire de Chimie de Coordination, A. Mari, J.-F. Meunier for their technical assistance in recording magnetic data, L. Rechinat for the fitting of the EPR radical spectrum and to Dr N. Roques for helpful discussion.

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