

1,2-Dicarbonyl Radicals with Exceptional Physiological and Chemical Stability

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Abstract: Organic radicals have been of great academic interest due to their unique reactivity and potential applicability; however, lack of stability and solubility continues to limit their application, especially in physiological conditions. For example, well-known aminoxyl radicals have half-life of a few minutes in physiological conditions due to biological redox active reagents, while shielding using polymeric or supramolecular protecting groups increases their half-life up to several hours. Here we designed and synthesized a new small molecular organic radical based on 1,2-dicarbonyl scaffold with exceptional stability. The presented radicals showed superior stability over present organic radicals towards physiological conditions (half-life of ~3000 hours) and even resistant towards chemically reducing, oxidizing, acidic, basic conditions, and high temperature, without additional protection.

Having an unpaired valence electron, organic radicals are often thermodynamically and kinetically unstable, making their isolation and structural characterization challenging. Since the ‘radical’ discovery of the triphenylmethyl radical – the first persistent organic radical – by Gomberg in 1900,¹ various strategies to stabilize organic radicals have been developed, leading to the successful discovery of other stable organic radicals (**Figure 1A**).² Despite the great potential of air- and water-stable organic radicals as electron transfer reagents, spin labels, or bio-imaging agents, they have limited stability under physiological conditions, which makes a major drawback for bio-application.³ For example, the most widely studied aminoxyl radicals (also known as nitroxyl radicals) are susceptible to decomposition in the presence of organic or biological reducing agents such as ascorbate, while triarylmethyl radicals readily react with oxidants such as peroxides.⁴ Therefore, development of new organic radical platform is desired with high stability towards physiological conditions.

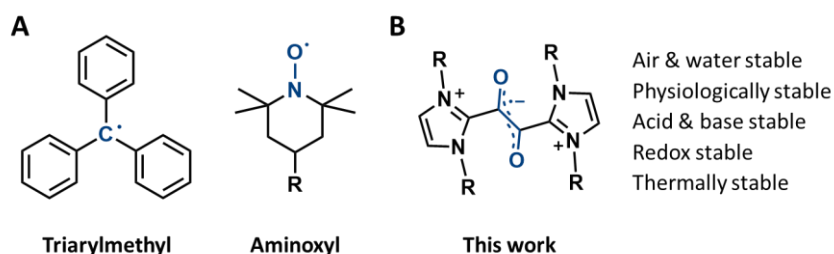


Figure 1. Examples of stable organic radicals.

(A) State of the art examples of most widely used organic radicals.

(B) Stable 1,2-dicarbonyl radicals from this work with the glyoxal radical anion core structure.

π -Conjugation enables the delocalization of spin density and hence increases radical stability.⁵ For example, glyoxal derivatives, as one of the simplest π -conjugated molecules, have been reported to generate corresponding 1,2-dicarbonyl radical anions,⁶ which are well-known redox active ligands. Several metal complexes containing 1,2-dicarbonyl radical anions have been reported;⁷ however, free 1,2-dicarbonyl radical anions are unstable, and have only been studied by spectroscopic and computational methods. For example, one electron reduction of phenylglyoxal derivatives produced the corresponding 1,2-dicarbonyl radical anions which were detected by electron paramagnetic resonance (EPR).⁶ Nonetheless, we assumed that, with appropriate steric and electronic stabilization, 1,2-dicarbonyl can be a versatile organic radical fragment.

N-heterocyclic carbenes (NHCs)⁸ are well known to facilitate the generation and utilization of unstable species,⁹ including main group¹⁰ and organic radicals, including carbonyl,¹¹ propargyl,¹² and aminyl¹³ derivatives, for example. In this context, we designed 1,2-dicarbonyl radical supported by two NHCs which may provide steric protection and delocalization of the spin density (**Figure 1B**).

Herein we report the synthesis and characterization of highly stable 1,2-dicarbonyl radicals with two imidazolium substituents. The presented radical has two major advantages over the widely used nitroxyl radicals: (i) it survives in the physiological reducing conditions while nitroxyl radicals rapidly decomposed to hydroxylamines, (ii) it has negligible spin density on the nitrogen and hydrogen atoms which results in a narrower EPR signal – and enables higher signal to noise ratio – compared to nitroxyl radicals. High stability and water solubility enabled the demonstration of those radicals as potential organic radical contrast agent candidates for magnetic resonance imaging.

Results and discussion

The 1,2-dicarbonyl radicals **2a^{••}** and **2b^{••}** can be easily synthesized from oxalyl chloride and the corresponding N-heterocyclic carbenes (NHCs) (**Figure 2A**). Under a N₂ atmosphere, the reaction of NHC **1a** (IMes; 1,3-dimesitylimidazol-2-ylidene) or **1b** (IDipp; 1,3-bis-(2,6-diisopropylphenyl)imidazol-2-ylidene) with substoichiometric amount of oxalyl chloride in THF produced [**2a^{••}**][Cl[−]] or [**2b^{••}**][Cl[−]], and subsequent anion exchange afforded [**2a^{••}**][BF₄[−]] or [**2b^{••}**][BF₄[−]], respectively, as deep purple solids. The reaction involves the formation of the dication intermediate [**2a²⁺**][Cl[−]]₂, followed by a spontaneous one electron reduction (See Supplementary Materials for detail).

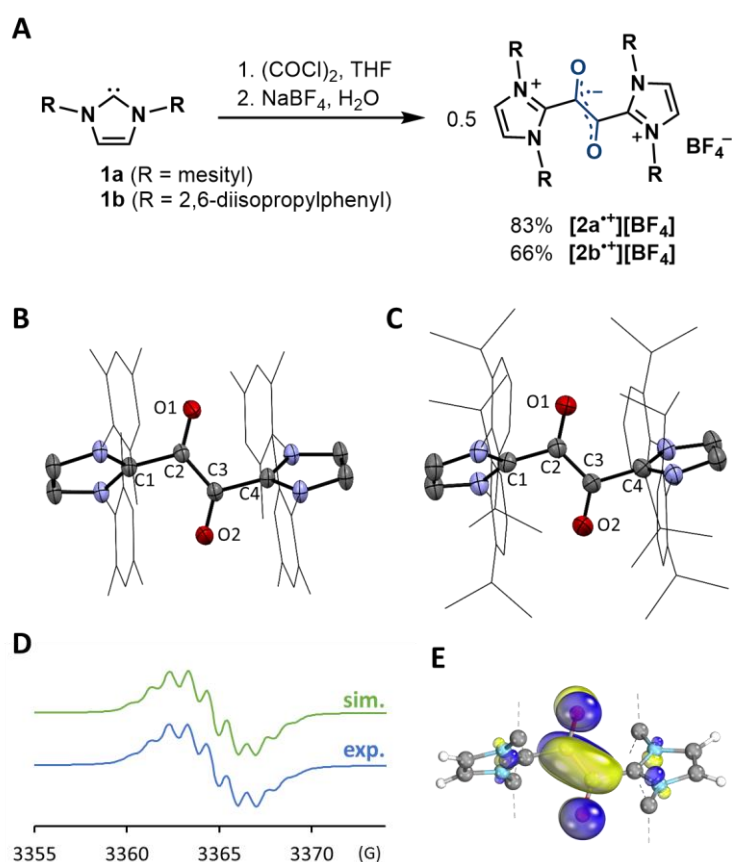


Figure 2. Synthesis and characterization of 1,2-dicarbonyl radicals.

(A) Synthesis of [**2a^{••}**][BF₄[−]] and [**2b^{••}**][BF₄[−]] from NHCs and oxalyl chloride.

(B and C) Solid-state structure of (B) [**2a^{••}**][BF₄[−]] and (C) [**2b^{••}**][BF₄[−]] from single crystal X-ray crystallography. The thermal ellipsoids are shown at the 30% probability level. Anions, hydrogen atoms, solvent molecules and disorders were omitted for clarity.

(D) Experimental (bottom) and simulated (top) EPR spectra of [**2a^{••}**][BF₄[−]] (g = 2.0060; hyperfine coupling constants: a(¹⁴N) = 3.0, 3.0, 2.6, 2.6 MHz).

(E) DFT calculated SOMO(α) of **2a^{••}** (M06/Def2-SV(P)); mesityl substituents were omitted for clarity.

Single crystals suitable for X-ray crystallography were grown by slowly evaporating the mixed water/acetone solutions, enabling the determination of molecular structures of [**2a^{••}**][BF₄[−]] and [**2b^{••}**][BF₄[−]] (**Figure 2B, 2C** and **Table S1**). The structural parameters for [**2a^{••}**][BF₄[−]] and [**2b^{••}**][BF₄[−]] are almost identical and well reproduced with DFT calculation on M06/Def2-SV(P)

level of theory (**Table S2**). The bond lengths of the central C₂O₂ unit indicate a bond order of 1.5 (O1–C2 1.245(2) Å; C2–C3 1.411(4) Å; C3–O2 1.245(2) Å for [2a^{•+}][BF₄[−]]). The planar structure of the central C₂O₂ unit also suggests π -delocalization of the radical (torsion angle for O1–C2–C3–O2: 172.8(3)° for [2a^{•+}][BF₄[−]]). The Wiberg bond orders were calculated, which were consistent with the single crystal X-ray structures (O1–C2 1.89; C2–C3 1.22; C3–O2 1.89 for [2a^{•+}][BF₄[−]], **Figure S3**).

Typically, NHC derived radicals¹⁴ have delocalized spin density due to strong π accepting ability of NHCs.¹⁵ In contrast, DFT calculations suggest that 2a^{•+} and 2b^{•+} are very rare examples of NHC-derived radicals with minimal delocalization of spin density over the NHC fragments. Very interestingly, 98% of spin density of 2a^{•+} is localized on the central C₂O₂ unit (O1 32%; C2 17%; C3 17%; O2 32%), with ca. ~1% of spin density for the NHC nitrogen atoms. Experimental EPR spectra of [2a^{•+}][BF₄[−]] and [2b^{•+}][BF₄[−]] were nearly identical, and successfully simulated with hyperfine coupling from four nitrogen atoms with small coupling constants ($a(^{14}\text{N}) = 3.0, 3.0, 2.6, 2.6$ MHz for [2a^{•+}][BF₄[−]]), in agreement with the small spin density on the nitrogen atoms (**Figure 2D**). DFT calculated singly occupied molecular orbital (SOMO) of 2a^{•+} (**Figure 2E**) well reproduced the typical Ψ_3 orbital of a conjugated system with four p orbitals (e.g. 1,3-butadiene). The UV-vis absorption spectrum of [2a^{•+}][Cl[−]] in distilled water at room temperature showed a peak at $\lambda_{\text{max}} = 472$ nm which was well approximated by time-dependent DFT calculation at M06/Def2-SV(P) level of theory (calculated $\lambda_{\text{max}} = 461$ nm corresponding to SOMO(α) to LUMO(α) transition, **Figure S10**). Interestingly, [2a^{•+}][Cl[−]] shows weak solvatochromism as its absorption was red-shifted in organic solvents ($\lambda_{\text{max}} = 510$ nm in acetonitrile; $\lambda_{\text{max}} = 521$ nm in dichloromethane, **Figure S11**).

The cyclic voltammograms of [2a^{•+}][BF₄[−]] and [2b^{•+}][BF₄[−]] were measured in acetonitrile, which showed reversible redox peaks at $E_{1/2} = 0.516$ and 0.490 V, respectively (vs. saturated Ag/AgCl electrode, **Figure 3B** and **Figure S6**). Chemical oxidation of [2a^{•+}][BF₄[−]] was performed using AgBF₄ as an oxidant, which produced the dication [2a²⁺][BF₄[−]]₂ (**Figure 3A**). Single crystal X-ray structure of [2a²⁺][BF₄[−]]₂ (**Figure 3C**) showed shortened O1–C2 (1.191(2) Å) and C3–O2 (1.201(2) Å), and elongated C2–C3 (1.536(5) Å) bonds, compared to [2a^{•+}][BF₄[−]]. This can be rationalized by considering the removal of the unpaired electron from the Ψ_3 shape SOMO that enhances the bonding O1–C2, C3–O2 and antibonding C2–C3 interactions. In addition, torsion angle for O1–C2–C3–O2 was significantly reduced to 156.9(4)° (compared to 172.8(3)° for [2a^{•+}][BF₄[−]]), which also indicates the decrease of C2–C3 π bonding interaction. Calculated Wiberg bond indices of 2a²⁺ also showed increased bond order for O1–C2 (2.27), C3–O2 (2.29), and decreased bond order for C2–C3 (0.97) compared to 2a^{•+} (**Figure S3**). On the other hand, electrochemical or chemical reduction of 2a^{•+} and 2b^{•+} to the corresponding neutral compounds was not successful.

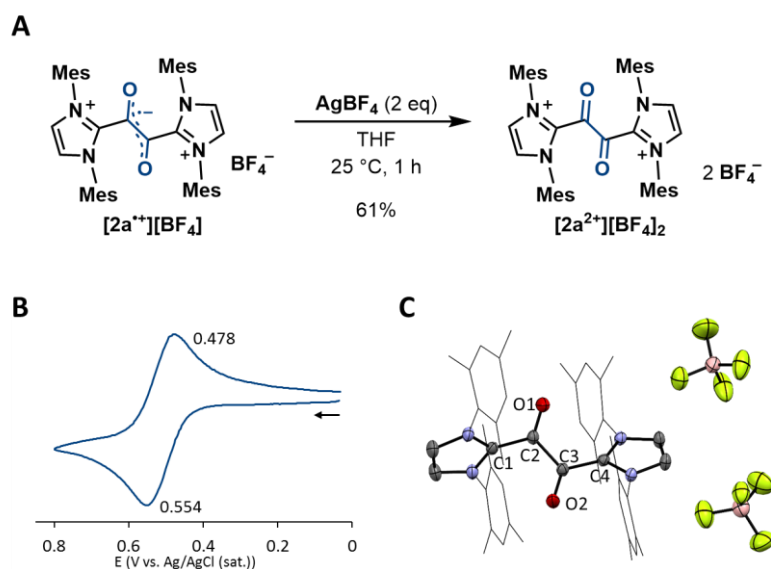


Figure 3. Redox behavior of the 1,2-dicarbonyl radical.

(A) One electron oxidation of [2a^{•+}][BF₄[−]] using silver tetrafluoroborate to produce [2a²⁺][BF₄[−]]₂.

(B) Cyclic voltammogram of [2a^{•+}][BF₄[−]] in acetonitrile with Bu₄NPF₆ (0.1 M) as the supporting electrolyte (scan rate = 0.1 V/s).

(C) Solid-state structure of [2a²⁺][BF₄[−]]₂ from single crystal X-ray crystallography. The thermal ellipsoids are shown at the 30% probability level. Hydrogen atoms, solvent molecules and disorders were omitted for clarity.

To test the stability of 1,2-dicarbonyl radicals under physiological conditions, UV-vis spectrum of $[2a^{**}][Cl^-]$ solution in potassium phosphate buffer (0.1 M, pH 7.4) was monitored, which showed a peak at $\lambda_{max} = 472$ nm. Surprisingly, $[2a^{**}][Cl^-]$ showed high stability as less than 3% of the radical was decomposed over 7 days which corresponds to the half-life of ~ 4000 hours (**Figure 4A** and **Figure S12A**). In addition, even in the presence of excess sodium ascorbate in the buffer solution, $[2a^{**}][Cl^-]$ showed high stability showing the half-life of ~ 3000 hours (**Figure S12B**). Furthermore, $[2a^{**}][Cl^-]$ survived in harsher conditions that most other organic radicals cannot (**Figure 4B** and **Figure S13**). For example, solution of $[2a^{**}][Cl^-]$ in horse blood serum showed ca. 2% decrease of UV-vis absorption over 500 minutes. $[2a^{**}][Cl^-]$ also showed exceptional stability towards highly basic or oxidizing conditions as in 0.1 M aqueous hydrogen peroxide or 0.1 M aqueous sodium hydroxide, less than 2% of $[2a^{**}][Cl^-]$ was decomposed over 500 minutes. In the presence of high excess (0.5 M) thiophenol in dichloromethane solution, $\sim 25\%$ decomposition of $[2a^{**}][Cl^-]$ was observed after 500 minutes, while under 0.1 M aqueous formic acid, $\sim 15\%$ of $[2a^{**}][Cl^-]$ was decomposed during 500 minutes. while. Notably, $[2a^{**}][Cl^-]$ showed ~ 2 hours of half-life even in highly acidic 0.1 M aqueous sulfuric acid solution.

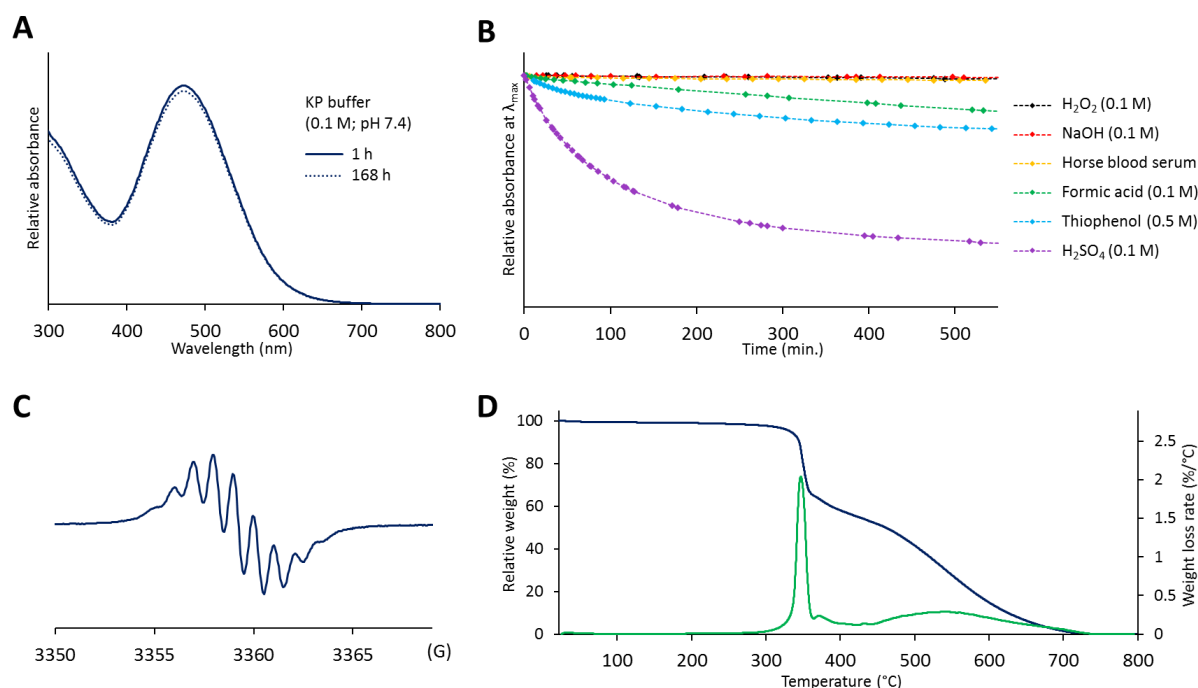


Figure 4. Stability of the 1,2-dicarbonyl radical.

(A) UV-vis spectra of 0.16 mM $[2a^{**}][Cl^-]$ in potassium phosphate buffer (0.1 M, pH 7.4) 1 h (solid line) and 168 h (dotted line) after dissolution. $\lambda_{max} = 472$ nm.

(B) Decay of 0.16 mM $[2a^{**}][Cl^-]$ in 0.1 M aqueous hydrogen peroxide (black, $\lambda_{max} = 472$ nm), 0.1 M aqueous sodium hydroxide (red, $\lambda_{max} = 472$ nm), horse blood serum (yellow, $\lambda_{max} = 488$ nm, serum(70%) mixed with distilled water(30%)), 0.1 M aqueous formic acid (green, $\lambda_{max} = 472$ nm), 0.5 M thiophenol in dichloromethane (blue, $\lambda_{max} = 521$ nm), and 0.1 M aqueous sulfuric acid (purple, $\lambda_{max} = 472$ nm).

(C) EPR spectra of $[2a^{**}][Cl^-]$ after heating for 6 hours at 200 °C.

(D) Thermal gravimetric analysis (dark blue) and differential thermal gravimetric (DTG) analysis (green) of $[2a^{**}][Cl^-]$ under air.

Thermal stability of $[2a^{**}][Cl^-]$ was also measured by heating the solid sample up to 200 °C over 6 hours, which showed no sign of decomposition, color change, or phase transition. The EPR spectrum of the heated $[2a^{**}][Cl^-]$ was identical to the spectrum of freshly synthesized sample (**Figure 4C**). Thermal gravimetric analysis (TGA) of $[2a^{**}][Cl^-]$ under air showed decomposition temperature of ca. 300 °C (**Figure 4D**), which is among the highest decomposition temperature reported for organic radicals.³

Having highly stable and water soluble organic radical in hand, we considered the application of $[2a^{**}][Cl^-]$ as an organic radical contrast agent for magnetic resonance imaging. Magnetic resonance imaging (MRI) is one of the most used biomedical imaging techniques;¹⁶ however, toxicity of gadolinium based contrast agents restricts their use in some patients with impaired kidney performance.¹⁷ Therefore, stable and water soluble organic radicals have been investigated as non-toxic alternative MRI contrast agents. Up to date, sterically hindered aminoxyl radicals show significant potential due to their accessibility and

functionalizability.¹⁸ Although aminoxyl radicals show reasonable stability toward water, they rapidly decompose to hydroxylamines under physiological conditions due to reducing agents such as ascorbate.¹⁹ For example, one of the most commonly used organic contrast agents, 3-carboxy-2,2,5,5-tetramethyl-1-pyrrolidinyloxy radical (3-CP) has a half-life of only ~2 minutes *in vivo*. Relaxation performance of $[2a^{**}][Cl^-]$ was measured at the magnetic field of 7 T (**Figure S18**), which showed longitudinal ($r_1 = 0.14 \text{ mM}^{-1} \text{ s}^{-1}$) and transverse relaxivity ($r_2 = 0.58 \text{ mM}^{-1} \text{ s}^{-1}$) comparable to or higher than other organic molecule-based contrast agents (e.g. $r_1 = 0.15 \text{ mM}^{-1} \text{ s}^{-1}$, $r_2 = 0.17 \text{ mM}^{-1} \text{ s}^{-1}$ for 3-CP).²⁰

In summary, highly stable and water soluble 1,2-dicarbonyl radicals $2a^{**}$ and $2b^{**}$ were synthesized and fully characterized. X-ray crystallography, EPR spectroscopy, and DFT calculation suggest the unpaired electron is located on the central C_2O_2 unit, which is a rare example of NHC-derived radicals with minimal delocalization of spin density over the NHC fragments. In addition, $2a^{**}$ and $2b^{**}$ showed high stability towards various chemical and physiological conditions. Interestingly, similar longitudinal relaxivity and higher transverse relaxivity was observed compared to the previously reported organic molecule-based contrast agents which makes these radicals promising candidates for organic radical MRI contrast agents.

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Author contributions

Y. K. designed and synthesized the 1,2-dicarbonyl radicals, performed experiments and characterization, and wrote the manuscript. J. E. B. assisted the synthesis of the radicals, and obtained experimental EPR spectrum of $[2a^{**}][BF_4^-]$ and $[2b^{**}][BF_4^-]$. G. Y. J. measured the stability of $[2a^{**}][Cl^-]$ in the buffer solutions. S. S. K. assisted the NMR relaxation experiments. H. S. measured the cyclic voltammograms. E. L. directed the project.

Notes

The authors declare the following competing financial interest: A patent application has been led through POSTECH on methods and reagents presented in this manuscript.

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