

Electrochemical Investigations on the NO-Releasing Property of Ruthenium Nitrosyl Complex

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Received: 21 September 2022;

Accepted: 14 October 2022;

Published online: 27 December 2022;

AJC-21077

In this study, the NO-donating property of [Ru(BPG)Cl(NO)]Cl (BPG = *N,N*-bis(2-pyridylmethyl)glycinato anion) *via* electrochemical activation was assessed. The synthesized BPG and [Ru(BPG)Cl(NO)]Cl were characterized by UV-Vis and FT-IR spectroscopy. To determine if NO may be released from the compound *via* one-electron reduction, cyclic voltammetric experiments in aqueous and non-aqueous solutions were performed using a three-electrode cell consisting of glassy carbon working electrode, Pt wire counter electrode and Ag/AgCl or Ag/Ag⁺ reference electrode. The [Ru(BPG)Cl(NO)]Cl complex showed two one-electron reversible reductions in dimethylformamide, which suggests decreased ability as NO donor. In aqueous solution at pH 2.0, [Ru(BPG)Cl(NO)]Cl exhibited a one-electron irreversible reduction, which could be assigned to a Ru-NO centered reduction. The irreversibility of the reduction could be due to NO labilization and suggests that [Ru(BPG)Cl(NO)]Cl could be a potential NO donor in acidic aqueous medium.

Keywords: Ruthenium nitrosyl, NO donor, Electrochemical analysis.

INTRODUCTION

When exposed to oxygen, nitric oxide (NO) is instantly converted into nitrogen dioxide (NO₂), a brown gas, which is a major contributor to air pollution [1]. Until late 1980s, it had been a recognized fact that NO was too toxic to have any significant biological or chemical roles [2]. However, NO is generated *in vivo* and functions as a messenger molecule for neurotransmission, immune system response and cardiovascular functions [3]. A rise in NO production has been discovered to be connected with a number of diseases such as sepsis, rheumatoid arthritis [4], inflammatory bowel disease [5] and asthma [6], while under-production could lead to hypertension [7], stroke and heart attack [8,9]. It is clear, therefore, that malfunction in the metabolism of this “simple” molecule has a significant impact to health. Following these discoveries, the desire to deliver NO at biological targets under physiological conditions has inspired research, particularly in the area of designed molecules that release NO upon demand [10-13].

For *in situ* delivery, NO donors have been developed which include organic nitrites and nitrates [14], nitrosothiols [15], diazeniumdiolates (NONOates) [10,16-19] and transition metal based compounds [20-23]. In recent years, it is a subject

of great interest, mainly because typical systemic donors such as glyceryl trinitrate, S-nitrosothiols and NONOates lack control for site-specific NO delivery [24]. Transition metal based compounds, particularly ruthenium nitrosyl complexes, have been postulated as a new class of NO-delivering agents [25] due to their high affinity for NO, solubility in water and thermo-dynamic stability [26] under laboratory and physiological [24] conditions. Small amounts of ruthenium are also found to be well-tolerated by the human body [27]. Furthermore, ruthenium displays chemical characteristics that are similar to those of iron present in the enzymes of biological systems [28] and their kinetic behaviour resembles that of platinum [29], with the advantage of lesser toxicity than cisplatin [30]. These characteristics give ruthenium based complexes the potential for medical applications [30]. Accordingly, NO may be liberated *in vivo* from ruthenium nitrosyl complexes *via* one-electron reduction [31,32], photolysis [33,34] or tissue-enzymatic action [35-37].

Ruthenium complex [Ru(BPMAA)Cl(NO)]⁺ (BPMAA = *bis*(2-pyridylmethyl)amineacetato anion) was found to release NO in acetonitrile when irradiated with UV-light [38]. Yet, its capacity to release NO in solution by electrochemical reduction remains to be assessed. In this study, the electrochemical

behaviour of $[\text{Ru}(\text{BPMAA})\text{Cl}(\text{NO})]\text{Cl}$ that relates to the ease by which it releases NO is to be established, through analysis of the redox potentials of the complex.

NO has been broadly established as having important roles in mammalian biology as a bioregulatory molecule and as a toxic agent against pathogen invasion [39-42]. Furthermore, numerous diseases have been linked to the over- and under-production of NO [43,44]. Since low (or high) NO levels can cause health issues, the development of drugs that can supply NO is of great interest [45].

While a number of ruthenium complexes are investigated as potential therapeutic NO scavengers by taking advantage of the high affinity of ruthenium for NO [46], ruthenium nitrosyl complexes are also being pursued as potential NO releasing agents [47,48] with pharmaceutical applications that range from treatment of cardiovascular dysfunction to tumor suppression through releasing cytotoxic NO [31]. This biomedical role places high importance to the understanding of the chemistry of Ru-NO complexes in terms of ease and mechanism of NO release and subsequent interaction of the delivered NO with biological systems. The release of NO is hypothesized to be induced by external stimulation such as one electron reduction. As the ligand framework in the coordination sphere of the complex affects the way electrons are moved [49], the present study seeks to explore this assertion.

This study aims to establish the NO-donating property of $[\text{Ru}(\text{BPMAA})\text{Cl}(\text{NO})]\text{Cl}$ complex. Specifically, it intends to analyze the electrochemical property of ruthenium nitrosyl complex in aqueous and organic solutions through cyclic voltammetry. The effect of pH on the electrochemistry of NO release in aqueous solution will also be assessed.

EXPERIMENTAL

All chemicals used were of reagent grade. IR spectroscopy was done using Nicolet iS-50 Analytical FT-IR spectrometer employing the diamond ATR as sampling technique. The absorption spectra were obtained *via* the Lasany LI 2800 UV-Vis spectrophotometer using a 1 cm quartz cuvette. Adjustments of pH of aqueous solution were done with Fisher Accumet pH meter model 610A. Lastly, cyclic voltammetric analysis was performed using Metrohm 797 VA Computrace voltammetric analyzer.

Synthesis of ruthenium nitrosyl complex: The complex $[\text{Ru}(\text{BPMAA})\text{Cl}(\text{NO})]\text{Cl}$ was synthesized according to the reported procedure [38]. In brief, the electrochemical measurements were done for aqueous and acetonitrile solutions (1×10^{-4} M) of $[\text{Ru}(\text{BPMAA})\text{Cl}(\text{NO})]\text{Cl}$ complex. The solutions were deaerated for at least 10 min prior to analysis. A three-electrode cell was employed, which include a glassy carbon working electrode, a platinum wire counter electrode and Ag/AgCl or Ag/Ag⁺ reference electrode. The supporting electrolyte consists of 0.1 M $\text{HC}_2\text{H}_3\text{O}_2/\text{NaC}_2\text{H}_3\text{O}_2$ buffer for aqueous experiment and 0.1 M tetra-*n*-butylammonium hexafluorophosphate for the non-aqueous experiment. The standards used were $[\text{Ru}(\text{NH}_3)_6]\text{Cl}_3$ and ferrocene for the aqueous and non-aqueous experiments, respectively. The cyclic voltammograms was recorded at varying scan rates.

RESULTS AND DISCUSSION

An average amount of 0.3612 g (~62% yield) of potassium *bis*(2-pyridylmethyl)glycinate (K(BPG)) was synthesized (Table-1). The compound was collected as a white solid powder that turned yellowish-green after standing for several weeks.

TABLE-1
AMOUNT AND PERCENT YIELD OF SYNTHESIZED K(BPG)

Trial	Amount (g)	Yield (%)
1	0.3749	64.15
2	0.3567	61.10
3	0.3521	59.94
Average	0.3612	61.73

Characterization studies: The FT-IR (KBr disc) spectrum of BPG (Fig. 1) showed the significant peaks at $\sim 1593 \text{ cm}^{-1}$ which was assigned to C=O stretching. The bands at $\sim 2830\text{-}2930 \text{ cm}^{-1}$ were due to the aliphatic C-H stretching, whereas aromatic C=C stretching was found at $\sim 1900\text{-}1600 \text{ cm}^{-1}$, the C-C-O stretching at around 1400 cm^{-1} and arom. C-H bending at $\sim 773 \text{ cm}^{-1}$. A broad band was observed at about $\sim 3400 \text{ cm}^{-1}$ which was attributed to -OH group. This implied that rotary evaporation employed in the workup was not able to completely remove moisture; hence the appearance of the H₂O peak. Additionally, two weak yet apparent peaks at $\sim 2360 \text{ cm}^{-1}$ were attributed to CO₂. Atmospheric light scattering did not prevent CO₂ from the appearance in the infrared spectrum.

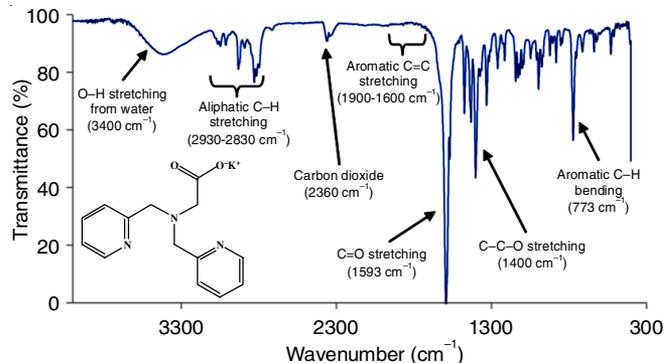


Fig. 1. FT-IR spectrum of potassium *bis*(2-pyridylmethyl)glycinate in KBr disc

For comparison, FT-IR spectra of the starting materials for the synthesis of K(BPG), *bis*(2-pyridylmethyl)amine and bromoacetic acid (Fig. 2) were also obtained. The FT-IR spectrum of K(BPG) appeared to be a combination of two reactants. The prominent C=O stretch of bromoacetic acid was found at $\sim 1725 \text{ cm}^{-1}$, which shifted to $\sim 1593 \text{ cm}^{-1}$ in K(BPG). The -OH stretch of the carboxylic acid was observed around 3000 cm^{-1} . For *bis*(2-pyridylmethyl)amine, the IR spectrum seemed to be similar with that of K(BPG). However, a closer examination revealed that the N-H stretching in *bis*(2-pyridylmethyl)amine was not present in K(BPG), suggesting that the tertiary amine of K(BPG) had been formed. Moreover, although the frequency of the NH bending in *bis*(2-pyridylmethyl)amine was found at almost the same region as that of C=O stretching of K(BPG), their huge differences in the peak intensities might

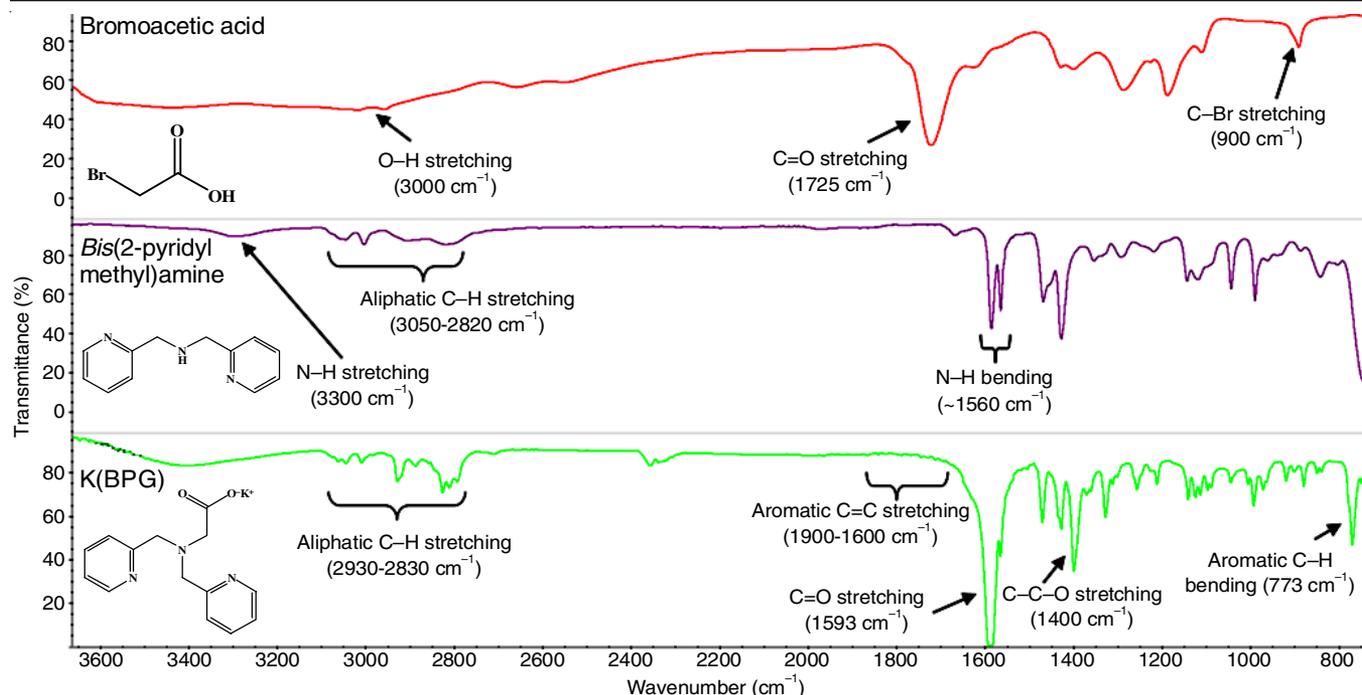


Fig. 2. Stacked FT-IR spectra of bromoacetic acid (KBr disc), bis(2-pyridylmethyl)amine (diamond ATR) and potassium bis(2-pyridylmethyl)glycinate (KBr disc)

be caused by the appearance of the various vibrational modes. It is also worth mentioning that the IR spectra of bis(2-pyridylmethyl)amine and K(BPG) were obtained through different sampling techniques (ATR for bis(2-pyridylmethyl)amine and KBr disc for K(BPG)). In general, these results suggested that K(BPG) was indeed formed by the synthetic reaction employed.

The electronic spectrum of K(BPG) in water showed the maximum absorption (λ_{\max}) at 260 nm (Fig. 3). The absorption peaks (Fig. 4) of [Ru(BPG)Cl(NO)]Cl in acetonitrile were found at 221 and 268 nm. Merkle [38] reported that these peaks at 226 and 365 nm, respectively. As seen, the peaks were blue-shifted (hypsochromic), especially for the 365 nm absorption.

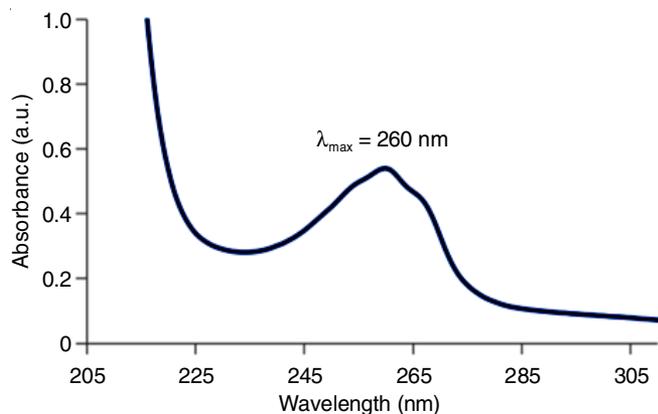


Fig. 3. UV-Vis spectrum of potassium bis(2-pyridylmethyl)glycinate (0.5 mM in water)

Electrochemistry: The [Ru(BPG)Cl(NO)]Cl complex was dissolved in DMF and then subjected to cyclic voltammetry in a modified electrochemical cell consisting of glassy carbon working electrode, platinum wire counter electrode and

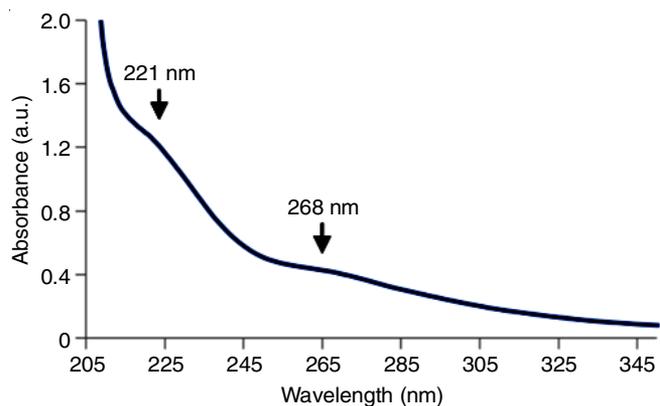


Fig. 4. UV-Vis spectrum of [Ru(BPG)Cl(NO)]Cl (0.02 mM in acetonitrile)

Ag/Ag⁺ (0.1 M in acetonitrile) reference electrode. All the potential measurements were plotted against Ag/Ag⁺ couple. The IR compensation was not performed due to the low scan rates employed (0.025-0.100 V/s). All the experiments were assumed to be diffusion-controlled. Furthermore, half-wave potentials were estimated by the average of the anodic and cathodic peaks:

$$E_{1/2} = \frac{E_{p,a} + E_{p,c}}{2}$$

The electrolytic medium, which contained 0.1 M tetra-*n*-butylammonium hexafluorophosphate in DMF, was transparent in the potential window selected for the analysis, according to the cyclic voltammogram. Hence, any signals were considered solely due to the test complex in the timescale of experiment. Scanning in the potential range of -0.035 V to -1.000 V (Fig. 5), the compound underwent reduction at $E_{p,c} = -0.700$ V (Wave II), with a shoulder peak at $E_{p,c} = -0.569$ V (Wave I). When the

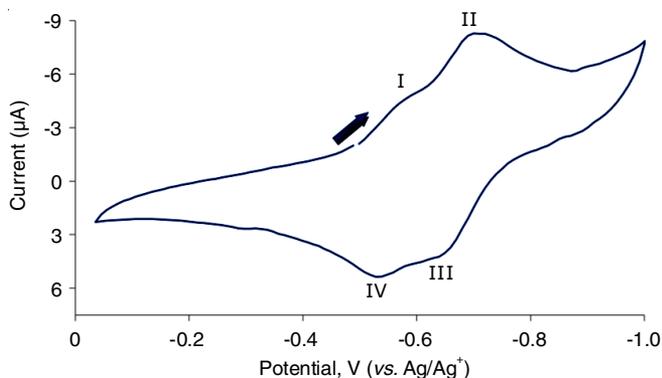
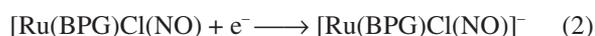


Fig. 5. Cyclic voltammogram of [Ru(BPG)Cl(NO)]Cl (8.35 mM in dimethylformamide containing 0.1 M hexafluorophosphate). Scan rate: 100 mV/s

scan was reversed, two oxidation peaks were observed: one at $E_{p,a} = -0.659$ V (Wave III) and another at $E_{p,a} = -0.539$ V (Wave IV). The overall shape of the voltammogram is indicative of not just one, but two reversible reductions. This electrochemical behaviour is characteristic of an E_rE_r mechanism, *i.e.* a reversible electron transfer reaction followed by another reversible electron transfer reaction. These two simultaneous one-electron transfer reactions were also independent of scan rates, which is another characteristic of an E_rE_r reaction.

Wave I may be assigned to the one-electron reduction of [Ru(BPG)Cl(NO)]⁺ to yield Ru(BPG)Cl(NO) (eqn. 1) and Wave II to another subsequent one-electron reduction forming [Ru(BPG)Cl(NO)]⁻ (eqn. 2). Wave III and IV may be assigned to the backward reactions of eqn. 2 and 1, respectively. Hence, [Ru(BPG)Cl(NO)]Cl underwent two one-electron processes in DMF solution:



From its electrochemical behaviour in DMF medium, it may be inferred that [Ru(BPG)Cl(NO)]⁺ has decreased capacity as potential NO donor in the timescale of the experiment, since the reversibility of its reduction entailed stability of the compound in the said solution. The standard, ferrocene (0.83 mM in DMF), showed a reversible one-electron reduction at $E_{1/2} = +0.014$ V for 0.100 V/s scan rate in the same experimental conditions with the test compound. The reported value for Fe(C₅H₅)₂²⁺/0 couple in DMF at 298.15 K and at the same scan rate was $E_{1/2} = 0.951$ V (*vs.* Ag/AgCl reference electrode). The large deviation from literature value may be attributed to the use of different reference electrode and unmatched experimental temperature.

Conclusion

In this study, potassium *bis*(2-pyridylmethyl)glycinate (K(BPG)) (where, BPG = *N,N*-*bis*(2-pyridylmethyl)glycinate anion) was synthesized and partially characterized *via* IR and UV-Vis spectroscopy. Using BPG as macrocyclic ligand, [Ru(BPG)Cl(NO)]Cl was synthesized and IR studies revealed the Ru-NO frequency at ~1896 cm⁻¹ that is characteristic for a linear nitrosyl in an octahedral complex. UV-Vis spectroscopy showed absorption peaks at 221 and 268 nm in acetonitrile. In order

to assess the NO-donating property of [Ru(BPG)Cl(NO)]Cl, electrochemical analyses were done in non-aqueous and aqueous solutions. It was found that the compound exhibited dissimilar redox behaviour in different media. In DMF solution, [Ru(BPG)Cl(NO)]⁺ elicited two one-electron reversible reductions at $E_{p,c} = -0.569$ V and $E_{p,c} = -0.700$ V. On the other hand, the complex showed a one-electron irreversible reduction at $E_{p,c} = -0.644$ V in aqueous solution at pH 2.0, which could be attributed to NO labilization. At a higher pH 7.40, oxidation of NO to NO₂ may have taken place, impeding an NO-centered reduction. Hence, it was concluded that [Ru(BPG)Cl(NO)]Cl may have decreased ability as NO donor in non-aqueous medium, while it could be a potential NO donor in the acidic aqueous medium.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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