

Short thesis for the degree of doctor of philosophy (PhD)

**The Synthesis, Characterization and Complex
Formation Reactions of 1,10-Phenanthroline-
Mono-*N*-Oxide Derivatives**

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Introduction and aim of the work

Over the past 50 years, numerous *N*-oxides of *N*-heteroaromatic compounds containing one or more nitrogen atoms have been synthesized. These compounds are used as oxidizing agents in organic syntheses, phase transfer catalysts, and as biomarkers for certain diseases. The *N*-oxidation of 1,10-phenanthroline (phen) exhibits unique characteristics compared to the reactions of other *N*-heteroaromatic compounds. While the mono-*N*-oxide of phen can easily be synthesized, it has been debated for a long time whether di-*N*-oxide formation is possible at all because the steric hindrance due to the rigid ring structure may prevent the oxidation of the second N atom.

In our research group, the oxidation of phen with peroxymonosulfate ion (PMS, oxone) was thoroughly investigated in a wide pH range. It was demonstrated that only 1,10-phenanthroline-mono-*N*-oxide (phenO) forms under acidic condition even when a large excess of PMS is used. However, as the pH increases, the formation of di-*N*-oxide also occurs, and it is further oxidized in consecutive reaction steps. These experimental observations were interpreted by considering the protonation of phenO and the formation of an intramolecular hydrogen-bonded structure that inhibits further oxidation steps in acidic solution. Such studies with substituted 1,10-phenanthroline derivatives had not been conducted previously.

The aim of my work was to synthesize a new family of compounds, 1,10-phenanthroline-mono-*N*-oxides, by oxidizing substituted 1,10-phenanthroline derivatives with oxone and to investigate the properties of these compounds. We wanted to study the kinetics of

1,10-Phenanthroline-Mono-N-Oxide Derivatives

the N-oxidation reactions in detail to determine the optimal experimental conditions for the synthesis of *N*-oxides. In the case of asymmetric phen derivatives, the formation of isomer mixtures is expected, so another objective was to develop separation methods suitable for isolating the isomers. Beyond the general characterization of the new *N*-oxides, we also intended to study the complex formation reactions of these compounds using pH-potentiometry, UV-spectrophotometry, and EPR spectroscopy.

Experimental methods

For our kinetic studies, we used a SHIMADZU 200 dual-beam spectrophotometer. The temperature dependence of the reaction rate was studied between 10.0 and 70.0 °C, with temperature control provided by the instrument's built-in thermostat.

pH-potentiometric studies were conducted using a Metrohm 785 DMP Titrand pH meter equipped with a Metrohm 6.0262.100 combined glass electrode. pH data were converted to hydrogen ion concentration following the method of Irving et al., so $\text{pH} = -\log[\text{H}^+]$.

For determining acid dissociation constants, spectrophotometric titrations were performed using Agilent Technologies Cary 8454 and Cary 60 UV-Vis spectrophotometers, using optical path lengths of 1.000 cm or 0.100 cm. To study the acid-base properties of structural isomers, we used ^1H NMR titrations that allowed us to determine acid dissociation constants without separating the corresponding isomers.

1D ^1H and ^{13}C NMR spectra were recorded to determine the structure and confirm the purity of oxidation products, along with 2D (^1H - ^1H and ^1H - ^{13}C) correlation techniques. Tetramethyl-silane (TMS) served as the internal standard ($\delta_{\text{TSP}} = 0.0$ ppm). Depending on the actual experiment, D_2O or CDCl_3 were used as solvent. NMR measurements were conducted using Bruker Avance DRX 360 and Bruker Avance I 400 MHz spectrometers.

Mass spectrometry was performed using a maXis II UHR ESI-QTOF MS (Bruker, Bremen, Germany). In these experiments, the concentration of the samples was always 0.1 mg/mL. The measured and simulated MS peaks were in excellent agreement.

For separating structural isomers, analytical HPLC was performed using a Waters 2695 Alliance system with a 2487 Dual λ

1,10-Phenanthroline-Mono-N-Oxide Derivatives

Absorbance detector or an AZURA KNAUER HPLC system. A Phenomenex Luna C18 100 Å 150 × 4.60 mm 3 µm column was used with a 1 mL/min flow rate. Preparative separations employed a modular HPLC system (YL9101 degasser, YL9110 pump, YL9120S UV/Vis Detector) with a Phenomenex Luna 10 µm Prep C18(2) 150A 250 × 21.20 mm 5 micron 00G-4324-P0 column at a 25 mL/min flow rate.

Solid-phase structure analyses were conducted using a Bruker D8 Venture (SC-XRD) diffractometer equipped with an INCOATEC IµS 3.0 dual (Mo, Cu) microfocus source (Mo-K α irradiation, $\lambda = 0.71073$ Å) and a Photon II Charge-integrating Pixel detector. The data were processed using Bruker APEX3 software, and absorption corrections were made with the MULTI-SCAN method. The structures were deposited in the Cambridge Crystallographic Data Centre (CCDC) under IDs 2075043, 2075044, 2075045, and 2075046.

Relaxometry measurements were performed at 25.0 °C using a Bruker Minispec MQ20 relaxometer operating at 0.49 T. T_1 relaxation times were measured using an inversion recovery pulse sequence, while T_2 times were determined with a Carr-Purcell-Meiboom-Gill (CPMG) sequence.

EPR spectroscopic studies were carried out in collaboration with the Research Centre for Natural Sciences (HUN-REN TTK) using a Bruker EleXsys E500 spectrometer on frozen samples at 77 K, cooled with liquid nitrogen.

Protonation constants of the synthesized ligands and stability constants of the complexes were estimated using the SUPERQUAD and PSEQUAD software.

New Scientific Results

1. The kinetics of the oxidation reaction between 7 different substituted 1,10-phenanthroline derivatives and oxone was studied in detail.

In addition to the base compound, we studied the oxidation of the following derivatives: 2,9-dimethyl-1,10-phenanthroline (DMP), 3,4,7,8-tetramethyl-1,10-phenanthroline (TMP), 4-methyl-1,10-phenanthroline (4MP), 5-methyl-1,10-phenanthroline (5MP), 5-nitro-1,10-phenanthroline (5NP), 5-chloro-1,10-phenanthroline (5CP).

1.1. We have demonstrated that only mono-N-oxides are formed with all 7 phenanthroline derivatives under acidic conditions. We determined the rate constants of the oxidation reactions and confirmed that the reactions can be described by an overall second-order rate equation.

The change in absorbance under pseudo-first-order conditions was monitored at a specific wavelength (360-380 nm range), where primarily the products contribute to this change. The kinetic curves were fitted to an exponential equation (1) by applying non-linear least squares method, and the apparent rate constants (k_{obs}) were determined for the reaction.

$$A = A_{\infty} - \Delta A e^{-k_{obs}t} \quad \Delta A = A_{\infty} - A_0 \quad (1)$$

A_0 , A_{∞} and A stand for the initial, final and the reaction time dependent absorbance, respectively. We observed similar kinetic characteristics in the reactions of all phenanthroline derivatives. Regardless of whether the starting 1,10-phenanthroline contains electron-withdrawing or electron-

donating substituent groups, only mono-*N*-oxides are formed under acidic conditions.

Figure 1 illustrates the dependence of the pseudo-first-order rate constants on the concentration of oxone in excess. In each case, the data can be fitted with a straight line starting from the origin, confirming that the oxidation is a first-order process with respect to oxone under these conditions.

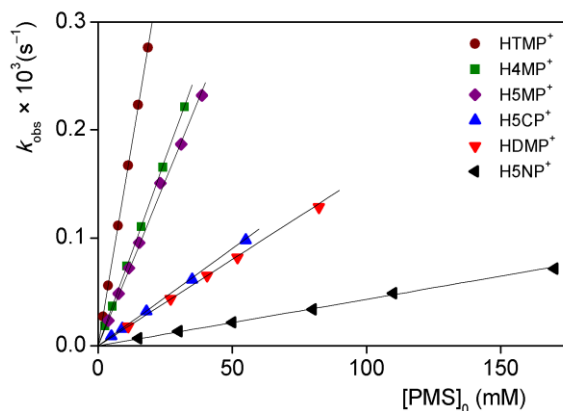


Figure 1. The dependence of the pseudo-first-order rate constants on the concentration of PMS; $[H_2SO_4] = 1.00\text{ M}$; $T = 25.0\text{ }^\circ\text{C}$

The reactions are first-order with respect to both the substrate and the oxidizing agent, i.e., these reactions behave analogously and can be characterized by an overall second-order rate equation (2).

$$v = k_{HL}[HL^+][PMS] \quad (2)$$

In the case of the symmetric derivatives, we also studied the pH dependence of the reaction and determined the rate constant for the reaction involving the deprotonated substrate (k_L). The rate constants are summarized in Table 1.

1.2. Based on the large negative activation entropy values of the reactions, we have concluded that the N-oxidation reactions proceed via oxygen atom transfer mechanism.

Under acidic conditions and with a large excess of oxone, the oxidation reaction was monitored at various temperatures. The kinetic curves at each temperature reach the same final absorbance within experimental error, suggesting that changing the temperature does not open new reaction paths in the system. The pseudo-first-order rate constants were determined by fitting the kinetic traces to equation (2). The temperature dependence of the second-order rate constants calculated from these values is shown in Figure 2.

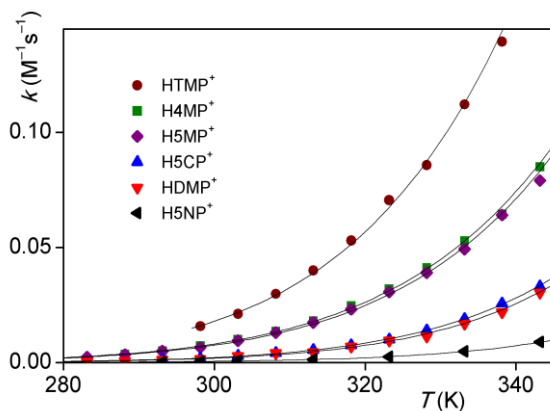


Figure 2. The temperature dependence of the rate constants for the reactions between phenanthroline derivatives and PMS. The experimental data are represented by markers, while the fitted curves based on the Eyring-Polányi equation are shown as continuous lines. $[H_2SO_4] = 1.014$ M.

In Figure 2, the fitting of the experimental data was performed based on the Eyring-Polányi equation (3).

$$k = \frac{k_0 T}{h} e^{\left(\frac{\Delta S^\ddagger}{R}\right)} e^{-\left(\frac{\Delta H^\ddagger}{RT}\right)} \quad (3)$$

The activation parameters are summarized in Table 1.

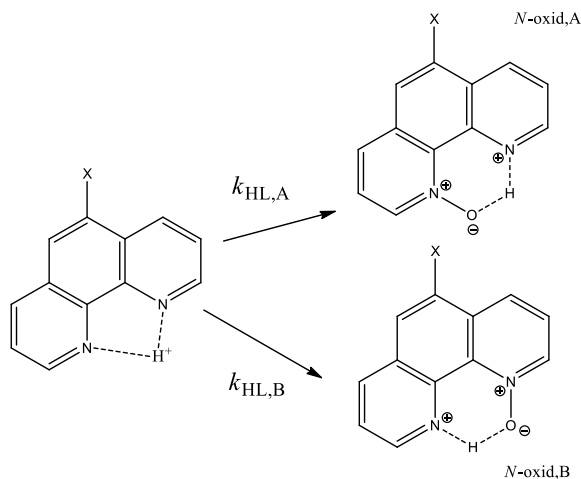
Table 1. *The rate constants for the oxidation of 1,10-phenanthroline derivatives with peroxomonosulfate ion (at 25.0 °C) and the associated activation parameters*

Substrate	k_{HL} 25.0 °C-on ($M^{-1} s^{-1}$)	ΔS^\ddagger [$Jmol^{-1}K^{-1}$]	ΔH^\ddagger [$KJmol^{-1}$]
HDMP⁺	$(1.59 \pm 0.06) \times 10^{-3}$	-121 ± 4	53 ± 1
DMP	18.0 ± 0.4^a	-139 ± 3	24.5 ± 0.9
HTMP⁺	$(1.50 \pm 0.03) \times 10^{-2}$	-134 ± 2	43.4 ± 0.7
TMP	10.1 ± 0.8^a	-105 ± 2	36.1 ± 0.7
H5MP⁺	$(4.6 \pm 0.1) \times 10^{-3}$	-137 ± 1	44.4 ± 0.4
H4MP⁺	$(5.2 \pm 0.2) \times 10^{-3}$	-136 ± 1	45.0 ± 0.4
H5CP⁺	$(1.68 \pm 0.08) \times 10^{-3}$	-124 ± 2	51.5 ± 0.6
H5NP⁺	$(0.43 \pm 0.01) \times 10^{-3}$	-126 ± 1	54.6 ± 0.3

^aThe rate constant of the reaction with the deprotonated substrate, k_L .

Earlier, our research group thoroughly investigated the mechanisms of oxidation reactions involving oxone with various substrates. It was established that the oxidation occurs either via oxygen atom transfer mechanism (which requires a higher degree of transient order in the transition state, characterized by a large negative activation entropy) or via one-electron oxidation mechanism (which requires less geometric rearrangement, and thus has a less negative activation entropy). The significantly negative ΔS^\ddagger values ($< -105 Jmol^{-1}K^{-1}$) suggest that the *N*-oxidation reactions studied here proceed via an oxygen atom transfer mechanism.

The *N*-oxidation of asymmetric substrates yields structural isomers, as illustrated in Scheme 1. The rate constants corresponding to the two reaction pathways cannot be determined independently by the applied kinetic method, but their ratio can be estimated based on the concentration ratio of the resulting isomers, which can be measured using ^1H NMR spectroscopy. The kinetic parameters listed in Table 1 correspond to the combined two reaction paths, thus $k_{\text{HL}} = k_{\text{HL,A}} + k_{\text{HL,B}}$.



Scheme 1. The general scheme for the formation of structural isomers.

1.3. We demonstrated a correlation between the basicity of 1,10-phenanthroline derivatives and their reactivity in N-oxidation reactions. The only deviation from the general trend was observed in the oxidation of the dimethyl derivative, which is attributed to the steric hindrance caused by the methyl substituents in positions 2 and 9.

It was confirmed that the logarithm of the rate constants for the N-oxidation reactions of 1,10-phenanthroline derivatives changes linearly with the pK_a of the substrates (Figure 3.). This trend can be explained by the pivotal role of the electron density on the nitrogen atom in the reaction with the electrophilic oxidizing agent. Accordingly, electron-donating substituents accelerate, while electron-withdrawing substituents slow the reaction.

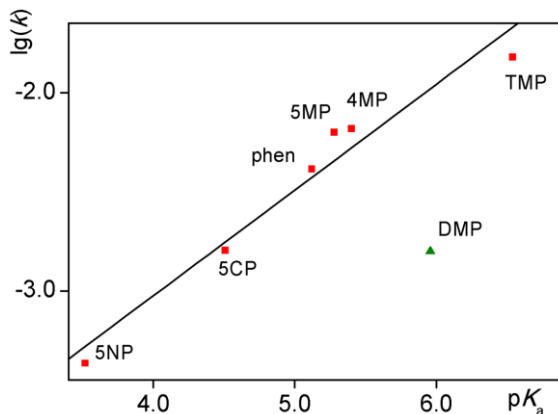


Figure 3. The logarithm of the rate constant (k_{HL}) for the N-oxidation reaction between 1,10-phenanthroline derivatives and HSO_5^- as a function of the acid dissociation constant (pK_a). $T = 25.0\text{ }^\circ\text{C}$, $I = 1.0\text{ M}$.

The rate constant obtained for the oxidation of DMP is approximately one order of magnitude smaller than the value expected

based on LFER (Linear Free Energy Relationships). In this case, it is likely that the methyl substituents at the 2 and 9 positions, which are close to the reaction center, sterically hinder the progress of the reaction.

2. We synthesized a new family of compounds by oxidizing 1,10-phenanthroline derivatives with oxone, producing and characterizing 11 different 1,10-phenanthroline mono-*N*-oxide derivatives.

2.1. *We developed a general method for the synthesis of N-oxides.*

Aqueous solutions of approximately 15 mM concentration were prepared for each 1,10-phenanthroline derivative, to which sulfuric acid was added to increase solubility and maintain an acidic pH (~2.0). Then an equivalent amount of PMS was added to the reaction mixtures which were stirred at 60 °C for 2 to 38 hours. After the reaction was complete and full conversion was achieved, the pH of the medium was adjusted by adding sodium hydroxide so that the 1,10-phenanthroline mono-*N*-oxide derivative was present in its deprotonated form (this also resulted in a color change that was visually noticeable). Then the product was removed from the aqueous phase by extraction with chloroform and the organic solution was dried with anhydrous Na₂SO₄. The remaining solution was filtered and then evaporated under vacuum. The yields are summarized in Table 2. For the structural isomers, the yield was determined from the combined mass of the two forms.

Table 2. *The yield values of the synthesized phenanthroline derivatives*

N-oxid	Yield [%]
phenO	86.6
DMPO	91.2
TMPO	88.1
5MPO and 6MPO	79.5
5NPO and 6NPO	92.1
5CPO and 6CPO	87.2
4MPO and 7MPO	82.8

In summary, we synthesized 11 different 1,10-phenanthroline mono-*N*-oxide derivatives, creating a new family of compounds which were not reported previously in the literature. For the separation of structural isomers formed from asymmetric substrates, we developed an analytical HPLC method. The separation is based on adjusting the pH of the eluent to between the pK_a values of the two isomers, such that one isomer is predominantly in the protonated form and the other is in the deprotonated form, ensuring their separation. The isolation of pure isomers was achieved by adapting the method to preparative HPLC.

2.2. We confirmed that the oxidation of all 1,10-phenanthroline derivatives yields exclusively mono-N-oxides under acidic conditions. The 11 mono-N-oxides were characterized using 1D NMR and 2D NMR, HRMS, and UV spectroscopy. Additionally, we determined the X-ray crystal structures of three of the products.

After the complete reaction of the oxidation processes, spectra recorded with various methods clearly confirm the full conversion of the substrates into the respective mono-N-oxides. The X-ray structures of phenO and DMPO are known from literature. During our work, we determined the structures of three additional mono-N-oxides: TMPO, 5CPO, and 6CPO. The determined N-O bond distances are in good agreement with the previously reported bond distance for phenO. It was concluded that π -stacking interactions between molecules, as well as hydrogen bonds formed with water molecules in the unit cells stabilize the crystal structures.

2.3. We found that, similarly to the 1,10-phenanthroline derivatives, the basicity of the synthesized N-oxides is significantly influenced by the electron-donating or electron-withdrawing properties of the substituents.

The acid-base properties of the starting 1,10-phenanthroline compounds and the synthesized phenO derivatives were examined by using various methods. Where the solubility of the compound allowed, pH-potentiometry was employed. In other cases, we used a combination of pH-potentiometry and UV-spectroscopy. The latter method was feasible due to the compound's high molar absorptivity, which allows for working with relatively dilute solutions. The pH-dependent spectra exhibit multiple isosbestic points, which is consistent with a simple

deprotonation process. For the determination of the pK_a , 4-5 wavelengths were selected where the absorbance changes were significant, and the experimental data were fitted simultaneously based on equation (4).

$$A = \frac{\varepsilon_{HA}[H^+] + \varepsilon_A K_a}{[H^+] + K_a} c_{tot} \quad (4)$$

where A is the absorbance measured at a given wavelength, ε_{HA} és ε_A are the molar absorptivities of the protonated and deprotonated forms, $[H^+]$ is the equilibrium concentration of hydrogen ion, K_a is the acid dissociation constant, and c_{tot} is the total concentration of the phenanthroline derivative. As an example, Figure 4 illustrates the experimental data and the fitting results for DMP.

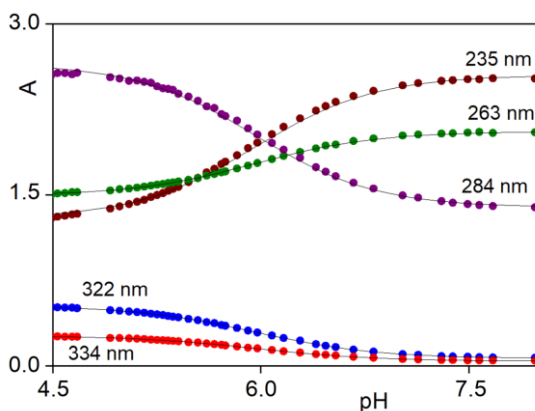


Figure 4. Determination of the acid dissociation constant for DMP by fitting the experimental data at five different wavelengths on the basis of equation (4). Measured absorbance (points) and fitted absorbance (continuous line) as a function of pH. $c_{DMP} = 1.0 \times 10^{-4} M$, $T = 25.,0 \text{ }^\circ C$, $I = 1.0 M$ (NaCl).

The acid dissociation constants of the structural isomers were determined using ^1H NMR spectroscopy without their separation. Proton NMR spectra of the isomer mixtures were recorded at various pH values. The chemical shifts corresponding to each isomer produced two well-separated sigmoid curves as a function of pH (Figure 5). This allowed for the independent determination of the $\text{p}K_{\text{a}}$ values. The experimental data were fitted using the non-linear least squares method based on equation (5).

$$\delta_{\text{pH}} = \frac{\delta_{\text{HA}}[\text{H}^+] + \delta_{\text{A}}K_{\text{a}}}{[\text{H}^+] + K_{\text{a}}} \quad (5)$$

where δ_{pH} is the chemical shift measured at a given pH, δ_{HA} and δ_{A} are the chemical shifts of the protonated and deprotonated forms, K_{a} is the acid dissociation constant, and $[\text{H}^+]$ is the hydrogen ion concentration.

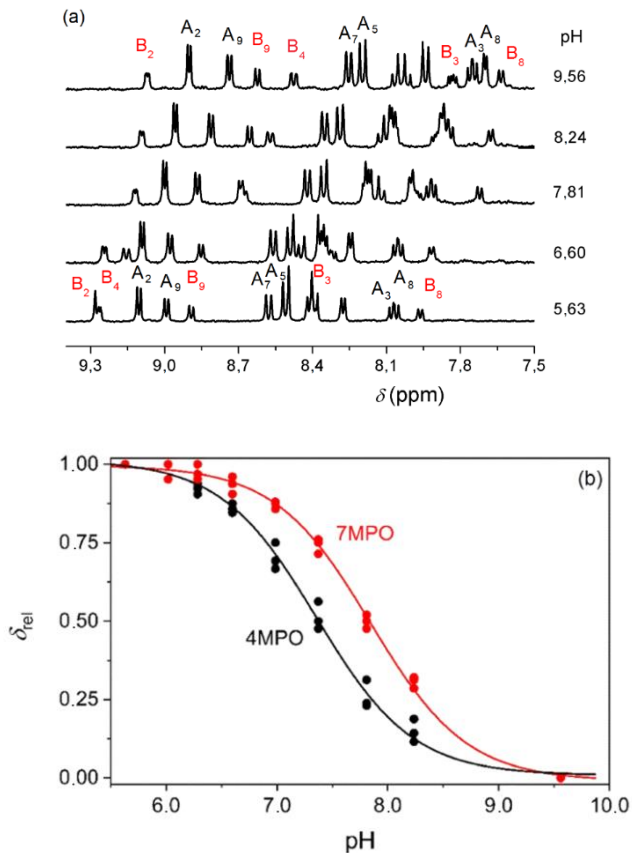


Figure 5. The determination of the acid dissociation constants for 4MPO and 7MPO using ^1H NMR spectroscopy without separating the isomers. (a): The ^1H NMR spectra of the isomer mixture as a function of pH. Peaks assigned to 4MPO are marked in black, while peaks assigned to 7MPO are marked in red. (b): The chemical shifts of selected ^1H NMR signals for the isomers as a function of pH. The peaks shown (markers) are: A₂ and A₉ for 4MPO, and B₂ and B₉ for 7MPO. The continuous lines represent the fitted curves. $c_{\text{tot}} = 1.0 \times 10^{-3}$ M, $T = 25.0$ °C, $I = 0.10$ M (NaCl).

The determined acid dissociation constants are summarized in Table 3.

Table 3. *The acid dissociation constants of the phenanthroline derivatives and their synthesized N-oxides, determined by various methods*

Ligand		Ligand	pK_a	Ligand	pK_a
phen	5.09 ± 0.01^a				
DMP	5.96 ± 0.01^b				
DMP	5.98 ± 0.04^c	phenO	7.10 ± 0.02^a		
TMP	6.53 ± 0.01^b	DMPO	8.83 ± 0.02^b		
TMP	6.48 ± 0.04^c	TMPO	9.03 ± 0.03^b		
5MP	5.28 ± 0.02^a	5MPO	7.40 ± 0.02^d	6MPO	7.50 ± 0.03^d
4MP	5.75 ± 0.04^b	4MPO	7.36 ± 0.03^d	7MPO	7.85 ± 0.02^d
5CP	4.51 ± 0.01^b	5CPO	6.40 ± 0.02^d	6CPO	6.14 ± 0.03^d
5NP	3.46 ± 0.01^b	5NPO	5.41 ± 0.04^d	6NPO	5.27 ± 0.03^d

^a Classic pH-potentiometry, $T = 25.0$ °C, $I = 1.00$ M (NaNO₃).

^b pH-potentiometry combined with UV-spectrofotometry.

$T = 25.0$ °C, $I = 1.00$ M (NaCl).

^c pK_a values obtained from kinetic measurements.

^d ¹H NMR titration. $T = 25.0$ °C, $I = 0.10$ M (NaCl).

It was found that compared to the parent compounds, the pK_a values of the N-oxides are 1.5 to 2.5 units higher. It is reasonable to assume that this is due to the formation of a relatively stable internal hydrogen bond between the partially negatively charged oxygen and nitrogen atoms in the N-oxides, which stabilizes the proton. This structure also explains why protonated N-oxides do not participate in further oxidation reactions with PMS. Additionally, we determined that the differences in acid dissociation constants are well understood in terms of the electron-donating and -withdrawing effects of the various

functional groups. The data indicates that the closer a functional group is to the protonation site, the more significant its effect is.

3. For three symmetric 1,10-phenanthroline mono-*N*-oxide derivatives (phenO, DMPO, and TMPO), we conducted a detailed study on their complex formation properties with several transition metal ions.

There is limited information available on the coordination chemistry properties of 1,10-phenanthroline-mono-*N*-oxide derivatives in the literature. However, we anticipate that these compounds would be suitable for forming stable complexes with transition metal ions. Therefore, we studied the complex formation reactions of Cu(II) and Ni(II) with the following mono-*N*-oxides: phenO, DMPO, and TMPO. Additionally, we determined the stability constants of Zn(II) complexes with phenO.

3.1. We established that phenO forms stable complexes with Cu(II), Ni(II), and Zn(II) ions, and the formation of bis complexes is preferred over mono complexes in all cases. We confirmed that phen forms more stable complexes compared to phenO. This can be explained by the fact that the latter ligands form the less favored six-membered chelate rings.

The pH potentiometric titrations were performed at metal ion-ligand concentration ratios of 1:2 and 1:3 in the entire pH range, while precipitation was observed at various pH values at 1:1 ratio in the slightly alkaline pH range. The stability constants are presented in Table 4. The data indicates that the ratio of the stepwise stability constants for the mono and bis complexes ($\log K_1/K_2$) is consistently lower than the statistically expected value, suggesting that the formation of bis complexes is favored.

Table 4. Stability constants of the complexes of phenO with copper(II), nickel(II), and zinc(II) ions. ($\log\beta_{\text{pqr}}$). $T = 25.0\text{ }^{\circ}\text{C}$, $I = 0.2\text{ M}$ (KCl)

$\log\beta_{\text{pqr}}$	phenO			
	Cu(II)	Cu(II)	Ni(II)	Zn(II)
ML	6.28 ± 0.04	$6.61 \pm 0.02^{\text{a}}$	5.0 ± 0.01	3.43 ± 0.01
ML(OH)				-5.06 ± 0.01
ML₂	12.98 ± 0.06	$13.13 \pm 0.02^{\text{a}}$	9.9 ± 0.08	6.49 ± 0.02
ML₂(OH)	1.98 ± 0.08	$1.98 \pm 0.08^{\text{a}}$		
M₂L₄(OH)₂	7.8 ± 0.03	$8.4 \pm 0.01^{\text{a}}$		
$\log K_1/K_2^{\text{b}}$	-0.4		0.1	0.37

^a Stability constants determined by EPR method

^b $\log K_1/K_2 = 2 \times \log\beta(\text{ML}) - \log\beta(\text{ML}_2)$.

The titration curves for Cu(II) can be interpreted by the formation of mono, bis, and mixed hydroxido complexes. UV-visible spectroscopy combined with pH-potentiometry, as well as EPR spectroscopy clearly exclude the formation of a tris complex. The stability of the mono complex is three orders of magnitude lower compared to the CuL^+ complex formed in the Cu(II)–phen system. This can be explained by considering that the significantly higher basicity of phenO compared to phen does not compensate for the destabilizing effect of the formation of a six-membered chelate ring. EPR results support the formation of complexes identified by pH-potentiometric and UV-visible spectroscopic measurements. Based on the hyperfine coupling constant (A) determined from EPR measurements, we concluded that the two nitrogen atoms are coordinated to the central metal ion in the equatorial plane in the bis-complex.

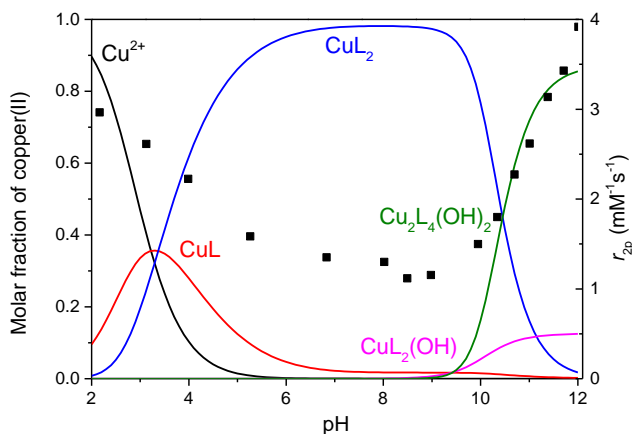


Figure 6. The concentration distribution of the Cu(II) – 1,10-phenanthroline-mono-*N*-oxide system as a function of pH, based on combined pH-potentiometric and EPR measurements at a 1:2 concentration ratio, and the pH-dependent T_2 relaxivity (■). $C_{phenO} = 3 \text{ mM}$, $I = 0.2 \text{ M (KCl)}$, $T = 25.0 \text{ }^\circ\text{C}$.

The pH dependence of the T_2 relaxivity of the system confirms that the relaxivity decreases with the formation of the bis complex, (Figure 6), but it does not drop to the relaxivity characteristic of the pure solvent. In the case of Cu(II) complexes, the proton exchange of axially coordinated water molecules, which are relatively distant from the metal ion, typically does not contribute to an increase in T_2 relaxivity. Therefore, the results lead to the conclusion that there is a coordinated water molecule in the equatorial plane of the bis complex. For the Ni(II) – phenO system, we confirmed that in the alkaline pH range, mixed hydroxido and tris- complexes are not formed. The pH-dependent UV-visible spectra show the formation of an absorption maximum at 480 nm, associated with a high-intensity $d-d$ transition for $\text{pH} > 5.0$. Based on this, we concluded that phenO coordinates via $2 \times (\text{N},\text{O})$ bonds in the bis

complex which is most likely square planar. By slowly evaporating the methanol solution of the alkaline sample, orange-colored crystals were obtained that were suitable for X-ray diffraction analysis.

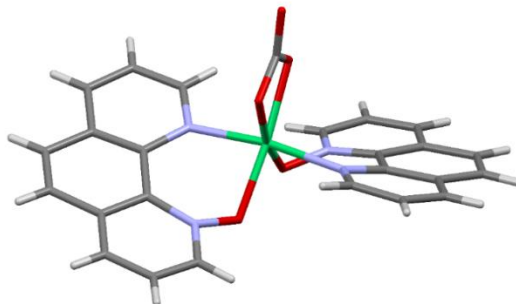


Figure 7. *The [Ni(phenO)₂CO₃] structure determined by X-ray diffraction.*

The results obtained from X-ray diffraction measurements support that the bis-complex features a $2 \times (\text{N,O})$ binding mode. The four donor atoms are positioned in the equatorial plane of the metal ion. However, the condensed aromatic rings are not coplanar, resulting in a distorted structure. In contrast to the Cu(II) and Ni(II) systems, the formation of relatively less stable ML^{2+} and ML_2^{2+} complexes occurs in the Zn(II)–phenO system. In this case, the formation of the bis complex is not significantly favored, and due to metal ion hydrolysis, it does not appear as a dominant species under the applied conditions.

3.2. It was confirmed that DMPO and TMPO participate in selective complex formation reactions. DMPO forms stable, water-soluble complexes only with Cu(II), while TMPO forms stable, water-soluble complexes only with Ni(II). No complex formation was observed in the case of Zn(II) with either ligands.

The stability constants of the complexes formed with the two ligands are summarized in Table 5.

Table 5. The stability constants of copper(II) and nickel(II) formed with DMPO and TMPO ($\log\beta_{pqr}$). $T = 25.0\text{ }^\circ\text{C}$, $I = 0.2\text{ M}$ (KCl).

$\log\beta_{pqr}$	DMPO		TMPO	
	Cu(II)	Ni(II)	Cu(II)	Ni(II)
ML	6.80 ± 0.01	N/A	N/A	5.56 ± 0.04
ML(OH)		N/A	N/A	-2.81 ± 0.04
ML(OH) ₂		N/A	N/A	-12.91 ± 0.02
ML ₂	12.00 ± 0.02	N/A	N/A	11.92 ± 0.02
ML ₂ (OH)	5.87 ± 0.03	N/A	N/A	
$\log K_1/K_2^a$	1.60	N/A	N/A	-0.8

$$^a \log K_1/K_2 = 2x \log\beta(\text{ML}) - \log\beta(\text{ML}_2).$$

DMPO forms a mono complex with copper(II) that is approximately half an order of magnitude more stable than the corresponding complex formed with phenO. This is likely due to the electron-donating effect of the methyl groups, which significantly increases the basicity of DMPO compared to phenO. This result is consistent with the observed difference in the pK_a values of the two ligands. For the bis-complexes, the stability constants show the opposite trend, which can be attributed to the steric repulsion of the methyl groups at positions 2 and 9 in DMPO.

Comparing the anisotropic EPR parameters for the bis complexes formed with Cu(II), it is that evident the A_z value is significantly smaller, while the differences in g_y and g_x are larger in the case of DMPO compared to phenO. This indicates a rhombic distortion in the geometry of the bis complex with DMPO. By slowly evaporating a methanolic solution of CuCl_2 and DMPO, we obtained crystals suitable for X-ray diffraction studies. The coordination of this ligand to the copper(II) ion through (N,O) donor groups is clearly demonstrated (see Figure 8). Overall, a square pyramidal geometry is formed. Due to the electron-donating repulsion of the methyl groups, the aromatic ring system of the ligand is twisted and out of the plane defined by the donor atoms.

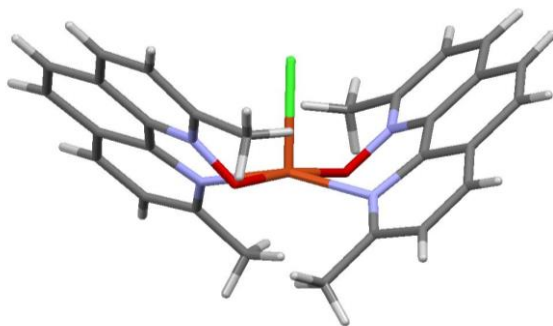


Figure 8. The $[\text{Cu}(\text{DMPO})_2\text{Cl}]^+$ structure determined by X-ray diffraction.

The formation of any Ni(II) complex with the DMPO ligand could not be confirmed by either pH-potentiometric or spectrophotometric methods in aqueous solution. We interpret this as consequence of the generally more rigid coordination sphere of the Ni(II) ion compared to the Cu(II) ion. The methyl substituents of DMPO sterically hinder the distortion of the planar *N*-heteroaromatic rings required for occupying the square planar coordination sites of Ni(II). The

formation of a highly distorted structure is therefore thermodynamically unfavorable.

In the Ni(II) – TMPO system, complex formation was studied using pH-potentiometry in combination with UV-visible spectrophotometric method. In this case, the formation of the bis complex is associated with significant spectral changes. The intense absorption band observed at 480 nm is attributed to the formation of a square planar, diamagnetic complex, which involves 2×(N,O) coordination mode.

Possible utilization of the results

In our work, we synthesized a new family of compounds from 1,10-phenanthroline derivatives. The fundamental properties of these new compounds have been described, but we have not explored their potential practical applications. It is well-known that *N*-oxides are used extensively in various chemical and biological systems. Based on this, it is anticipated that the compounds described here may also be well-utilized for similar purposes.

A specific feature of the *N*-oxides formed from 1,10-phenanthroline derivatives is their relatively rigid structure, where the position of the N–O bond relative to the other *N* atom is "fixed." This property allows these compounds to engage in selective interactions with various biomolecules in biological systems compared to other *N*-oxides. This opens the way for the development of more useful markers and biological agents than those previously described.

The use of *N*-oxides as ligands theoretically opens additional application possibilities. These complexes may be suitable for catalyzing various reactions. Based on previous considerations, specific interactions cannot be ruled out in these cases either. A particularly interesting question is what kind of complexes form with multivalent metal ions and what reactions they might participate in. In this regard, the redox reactions of 1,10-phenanthroline complexes, which are well-documented in the literature, may serve as benchmarks. The redox properties of complexes formed with *N*-oxides are likely to depend significantly on the quality and number of substituents on the aromatic ring. This theoretically creates the possibility for complexes that meet specific

1,10-Phenanthroline-Mono-N-Oxide Derivatives

expectations in redox systems. From an electrochemical perspective, an especially interesting possibility would be the modification of electrodes using complexes formed with *N*-oxides.



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List of publications related to the dissertation

Foreign language scientific articles in international journals (3)

1. Lihi, N., May, N. V., Udvardy, A., **Najóczki, F.**, Bonczidai-Kelemen, D., Diószegi, R., Vargáné Szalóki, D., Sánta, S. O., Fábíán, I.: Complexes of 1,10-phenanthroline-mono-N-oxides with copper(II) and nickel(II) in aqueous solution and solid phase.
Inorg. Chim. Acta. 557, 1-11, 2023. ISSN: 0020-1693.
DOI: <http://dx.doi.org/10.1016/j.ica.2023.121715>
IF: 2.7
2. **Najóczki, F.**, Szabó, M., Lihi, N., Udvardy, A., Fábíán, I.: Synthesis and Characterization of 1,10-Phenanthroline-mono-N-oxides.
Molecules. 26 (12), 1-19, 2021. ISSN: 1420-3049.
DOI: <http://dx.doi.org/10.3390/molecules26123632>
IF: 4.927
3. **Najóczki, F.**, Bellér, G., Szabó, M., Fábíán, I.: Substituent effect on the N-oxidation of 1,10-phenanthroline derivatives by peroxomonosulfate ion.
New J. Chem. 41 (18), 9947-9953, 2017. ISSN: 1144-0546.
DOI: <http://dx.doi.org/10.1039/C7NJ01860F>
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