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Redox Activity of Ce(IV)-Substituted Polyoxometalates toward Amino Acids and Peptides

Shorok A. M. Abdelhameed, Laurens Vandebroek, Francisco de Azambuja, and Tatjana N. Parac-Vogt*

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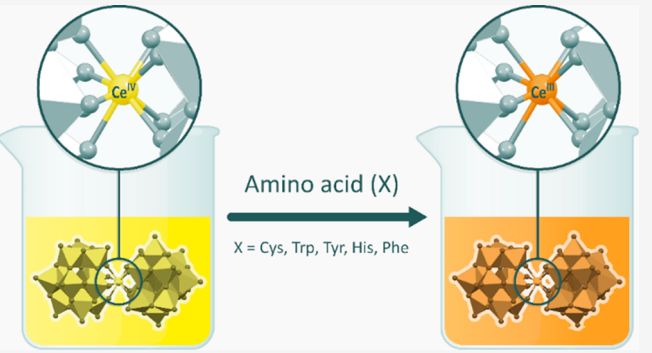
ABSTRACT: Redox reactions between polyoxometalates (POMs) and biologically relevant molecules have been virtually unexplored but are important, considering the growing interest in the biological applications of POMs. In this work we give a detailed account on the redox behavior of Ce^{IV}-substituted polyoxometalates (Ce^{IV}-POMs) toward a range of amino acids and peptides. Ce^{IV}-POMs have been shown to act as artificial proteases that promote the selective hydrolysis of peptide bonds. In presence of a protein, a concomitant reduction of Ce^{IV} to Ce^{III} ion is frequently observed, leading us to examine the origins of this redox reaction by first using amino acid building blocks as simple models. Among all of the examined amino acids, cysteine (Cys) showed the highest activity in reducing Ce^{IV}-POMs to Ce^{III}-POMs, followed by the aromatic amino acids tryptophan (Trp), tyrosine (Tyr), histidine (His), and phenylalanine (Phe). While the redox reaction with Cys afforded the well-defined product cystine, no oxidation products were detected for the Trp, His, Tyr, and Phe amino acids after their reaction with Ce^{IV}-POMs, suggesting a radical pathway in which the solvent likely regenerates the amino acid. In general, the rate of redox reactions increased upon increasing the pD, temperature, and ionic strength of the reaction. Moreover, the redox reaction is highly sensitive to the type of polyoxometalate scaffold, as complexation of Ce^{IV} to a Keggin (K) or Wells–Dawson (WD) polyoxotungstate anion resulted in a large difference in the rate of redox reaction for both Cys and aromatic amino acids. The reduction of Ce^{IV}K was at least 1 order of magnitude faster in comparison to Ce^{IV}WD, in accordance with the higher redox potential of Ce^{IV}K in comparison to Ce^{IV}WD. The reaction of Ce^{IV}POMs with a range of peptides containing redox-active amino acids revealed that the redox reaction is influenced by their coordination mode with Ce^{IV} ion, but in all examined peptides the redox reaction is favored in comparison to the hydrolytic cleavage of the peptide bond.



INTRODUCTION

Cerium is among the most abundant rare-earth elements[1,2] and has found extensive uses in materials chemistry,[3,4] catalysis,[5] and synthetic organic chemistry.[6,7] In catalysis, the application of cerium compounds, particularly Ce^{IV}, has been motivated either by its prominent redox properties ($E^{\circ}_{Ce^{IV}/Ce^{III}} \approx +1.44$ V vs NHE)[2,8,9] or its pronounced Lewis acidity.[10,5,11] With regard to reactions performed in water, which are highly relevant for bioinorganic applications such as dephosphorylation[12] and peptide bond hydrolysis reactions,[5] the use of simple Ce^{IV} salts as catalysts has been largely limited to acidic media,[2] as in neutral and alkaline pH conditions the formation of insoluble hydroxide gels drastically limits their reactivity.[5,11] This tendency to form insoluble gels can be circumvented by complexing the Ce^{IV} cation to ligands such as polyoxometalates (POMs). POMs are a large and diverse group of early-transition-metal–oxygen anionic clusters with unique chemical and physical properties,[13−15] and imbedding Ce^{IV} in POMs results in rather robust, selective, and homogeneous catalysts with a wide range of applications.[16−20]

While Ce^{IV}-substituted POMs (Ce^{IV}-POMs) have been established as catalysts for different organic transformations, their application as catalysts for biologically relevant reactions has been scarcely explored. Incorporation of redox or Lewis acidic metals into POM scaffolds results in a subgroup known as metal-substituted POMs (MS-POMs), which is considered to be an effective strategy to tune POM reactivity toward biomolecules.[21,22] In recent years, our group has intensely studied the interactions of MS-POMs with biomolecules by performing crystallographic[23,24] and spectroscopic[25−27] studies, as well as investigating MS-POM hydrolytic activity toward phosphodiester[28,29] and peptide bonds.[30−35] In this context, we have disclosed the selective hydrolysis of hen egg white

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lysozyme (HEWL),[36] transferrin (Tf),[19] and cytochrome *c* (cyt *c*)[30,37] proteins under mild conditions using $K_{10}[Ce^{IV}(PW_{11}O_{39})_2]$ as a catalyst. Interestingly, partial reduction of the Ce^{IV}-POM to the hydrolytically inactive Ce^{III}-POM was also detected in the course of protein hydrolysis.[36,38] In the absence of a protein, the Ce^{IV}-POMs were stable in aqueous solution,[29] suggesting that the protein itself was responsible for the observed reduction. In nature, proteins engage in several oxidation−reduction reactions mainly through their redox-active amino acids.[39] This feature is also the basis of redox proteomics, a branch of proteomics which is used to identify oxidized proteins and determine the extent and location of oxidative modifications.[40]

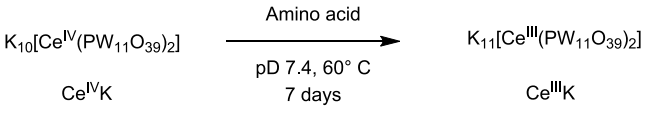
In this context, we realized that optimization of Ce^{IV}-POM artificial protease activity required a deeper molecular level understanding of its redox activity in the presence of proteins. Furthermore, redox reactions between MS-POMs and proteins have been virtually unexplored, which is an important knowledge gap in the literature considering the growing interest in the biological applications of POMs.[22,24,33,37,41,42] Moreover, the versatility of cerium in catalysis and the limited data available on Ce-POM chemistry involving proteins and other biomolecules further inspired us to provide this detailed account of the redox reactivity between Ce^{IV}-POMs and amino acids and peptides. Approaches to tune the redox activity of Ce^{IV} ions toward amino acids by adjusting the reaction parameters and the nature of the POM ligand have been also examined.

RESULTS AND DISCUSSION

Screening Redox Activity of Ce-POM toward Amino Acids. The reduction of Ce^{IV} ion in $K_{10}[Ce^{IV}(PW_{11}O_{39})_2]$ ($Ce^{IV}K$) to Ce^{III} results in $K_{11}[Ce^{III}(PW_{11}O_{39})_2]$ ($Ce^{III}K$) and can be conveniently detected by ^{31}P NMR spectroscopy. $Ce^{IV}K$ is characterized by a single ^{31}P peak at −13.4 ppm, while $Ce^{III}K$ exhibits a ^{31}P signal at −18.7 ppm.[43] Thus, ^{31}P NMR spectroscopy can be used as an excellent tool to investigate the redox activity of $Ce^{IV}K$ in the presence of selected naturally occurring amino acids and short peptides.

Using reaction conditions similar to those for the hydrolysis reaction performed previously,[36] we initially tested the redox activity of $Ce^{IV}K$ in the presence of naturally occurring amino acids (Table S1). Among all examined amino acids, only cysteine (Cys), tryptophan (Trp), tyrosine (Tyr), histidine (His), and phenylalanine (Phe) caused the detectable reduction of $Ce^{IV}K$ to $Ce^{III}K$ (Scheme 1). The highest activity was observed in the presence of Cys, which resulted in ca. 50% conversion of $Ce^{IV}K$ to $Ce^{III}K$ directly after mixing at room temperature. For comparison, upon addition of Trp and Tyr only 14% and 7% of $Ce^{IV}K$ was reduced, respectively, directly after mixing, and addition of His and Phe showed no evidence of $Ce^{IV}K$ reduction at room temperature. In fact, reactivity in the presence of His (10%) and Phe (5%) was only observed after 7 days of incubation at 60 °C. Although the redox potential of amino acids depends on the medium, these results follow a general trend that can be extracted from the literature, with the redox potential increasing in the following order: Cys[44,45] < Trp ≈ Tyr[46−48] < His[49,48,50] < Phe.[51] Given the striking difference in the $Ce^{IV}K$ reduction in the presence of different amino acids, a detailed kinetic study was performed with each amino acid that exhibited a redox behavior. The influence of several reaction parameters such as pD, temperature, concentration, and ionic strength on the reduction rate of Ce^{IV}POM was also investigated.

Scheme 1. Screening of the Redox Activity of $Ce^{IV}K$ toward Amino Acids[b]

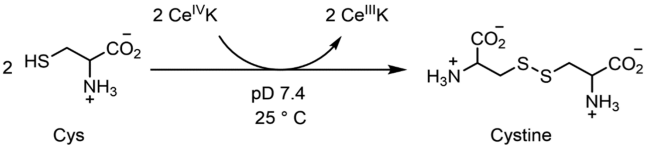


Amino acid	$Ce^{III}K$ (%)
Cys	>99
Trp	>99
Tyr	>99
Phe	5
His	10
Other AA[a]	0

[a]Other amino acids tested: Gly, Ala, Leu, Pro, Met, Asp, Ser, Thr, Asn, Arg. [b]Reaction conditions: $Ce^{IV}K$ (2 mM), amino acid (2 mM), pD 7.4, 60 °C, 7 days (^{31}P NMR yield).

Redox Reaction between $Ce^{IV}K$ and Cys. Among all amino acids that induced cerium reduction, cysteine provided the fastest reaction rates, and it was the only amino acid to form a clear product: i.e., cystine. Given the high reactivity observed in the initial screening experiments, the reaction between $Ce^{IV}K$ and Cys was studied at room temperature (Scheme 2). When equimolar amounts of $Ce^{IV}K$ and Cys were mixed, at pH 7.4 and 25 °C, a fast reduction to $Ce^{III}K$ was detected by ^{31}P NMR spectroscopy (Figure 1a). The 50% amount of $Ce^{IV}K$ was observed directly after mixing and recording the ^{31}P NMR spectrum, and complete reduction was achieved after 2.5 h. Concomitant with the reduction of $Ce^{IV}K$, the oxidation of Cys to cystine was observed by ^{1}H NMR by the decrease in peaks from Cys (δ 3.00−3.13 and 3.96−3.99 ppm), and the appearance of new peaks (δ 3.17−3.23, 3.38−3.44, and 4.11−4.14 ppm), which could be unambiguously assigned to cystine (Figure 1b).[52]

Scheme 2. Oxidation of Cys to Cystine by $Ce^{IV}K$



The rate of the reaction between $Ce^{IV}K$ and Cys followed a second-order kinetics, which is consistent with previous studies on the oxidation of thiols to disulfide products.[53−55] Interestingly, the rate constant (k_{obs}) of $Ce^{IV}K$ reduction ($(35 \pm 0.03) \times 10^{-3}$ mM^{-1} min^{-1}) was found to be nearly 2.5 times faster than k_{obs} for Cys oxidation ($(13 \pm 0.005) \times 10^{-3}$ mM^{-1} min^{-1}). This curious discrepancy suggests that the cysteinyl radical might be partially regenerated by the reaction medium. Consistent with this hypothesis, we still observed ~20% of Cys unconverted in solution after the reduction of $Ce^{IV}K$ was complete. On the other hand, this observation could be attributed to the ability of Ce^{IV} ions to break a disulfide bridge and oxidize it to other products,[56] since a disulfide bond is considered to be one of the weakest covalent bonds.[57] However, no other oxidation products were detected in the reaction mixture, and no other POM-related products were detected by ^{31}P NMR. This is consistent with the lack of

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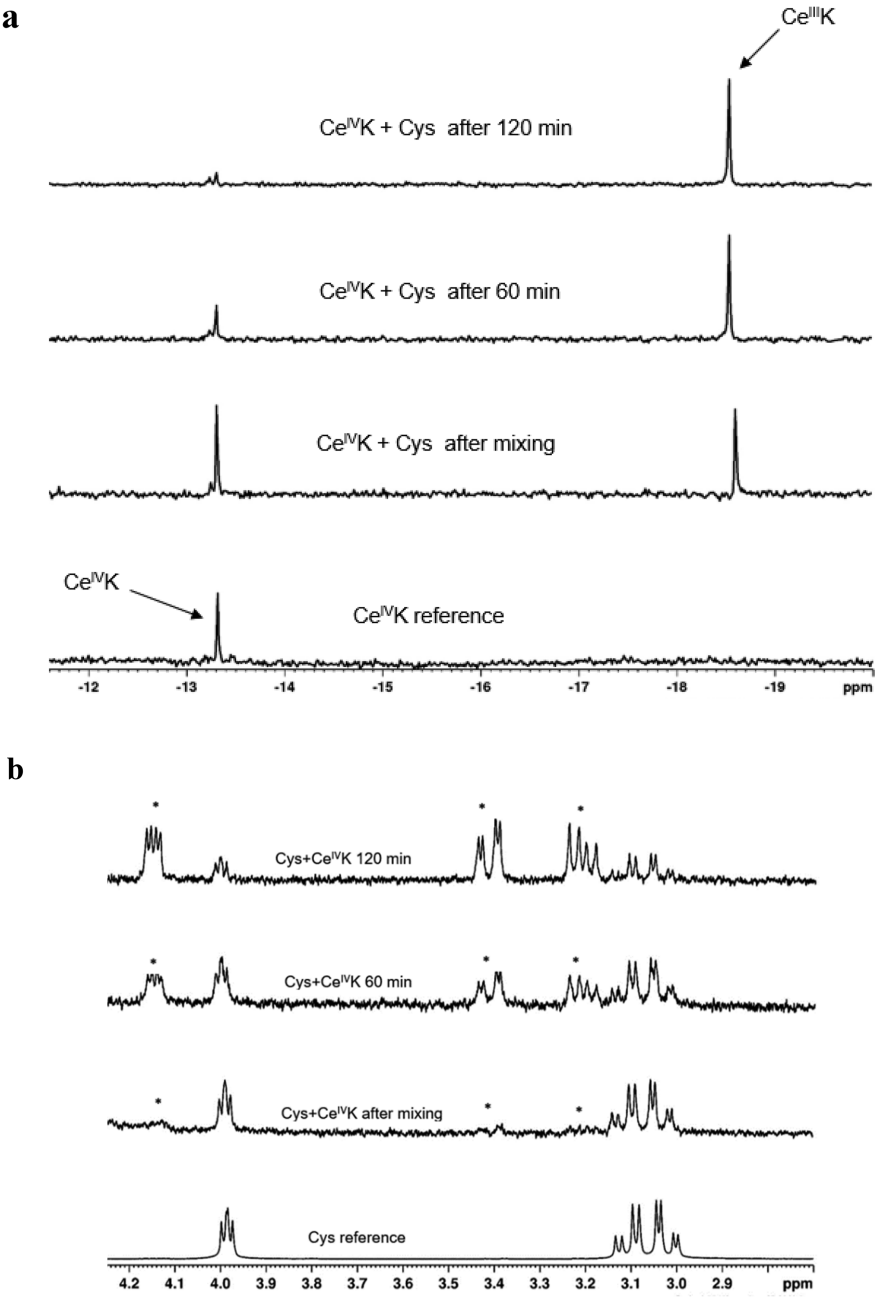

Figure 1. Cys and $Ce^{IV}K$ redox reaction at pD 7.4 and 25 °C: (a) ^{31}P NMR spectra showing fast reduction of of $Ce^{IV}K$ to $Ce^{III}K$; (b) ^{1}H NMR spectra evidencing Cys oxidation to cystine along with the cerium reduction (asterisks denote cystine peaks).

reactivity with methionine (Met) observed in the initial screening (Table S1). Unlike Ce^{IV} salts,[58] $Ce^{IV}K$ showed no redox activity toward the thioether group of methionine (Met) amino acid, which could be ascribed to the fact that incorporation of Ce^{IV} ion into the POM ligand leads to formation of a milder oxidant that is unable to oxidize a thioether group.[59,60] This indicates that $Ce^{IV}K$ is probably not involved in other side reactions and again suggests that regeneration of the cysteinyl radical is the probable cause of the distinct rate constants between $Ce^{IV}K$ reduction and Cys oxidation.

The formation of cystine likely takes place through the homocoupling of cysteinyl radicals (Cys-S$^{\bullet}$) (Scheme 3), which are probably formed through the oxidation of a cysteinyl anion (Cys-S^{-}) by $Ce^{IV}K$.[61] This oxidation has been reported as the rate-determining step of this reaction.[55] Given the dependence of the reaction rate on the availability of the Cys-S^{-}, we probed the effect of pD on the redox reaction kinetics. Within the examined range of pD (3.4−8.4), the rate of the reaction was found to linearly increase upon an increase in pD.

Scheme 3. Simplified Mechanism for the Formation of Cystine in the Redox Reaction Between CeIVK and Cys

$$\text{Cys-SH} \rightleftharpoons \text{Cys-S}^{-} + \text{H}^{+} \quad (1)$$

$$\text{Cys-S}^{-} + \text{Ce}^{IV}\text{K} \rightarrow \text{Cys-S}^{\bullet} + \text{Ce}^{III}\text{K} \quad (2)$$

$$2\text{Cys-S}^{\bullet} \rightarrow \text{Cys-S-S-Cys} \quad (3)$$

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This is in full agreement with the simplified proposed mechanism in Scheme 3, in which the production of Cys-S$^-$ species in step 1, which later produces the cysteinyl radical, is favored at low [H$^+$] (Figure 2).

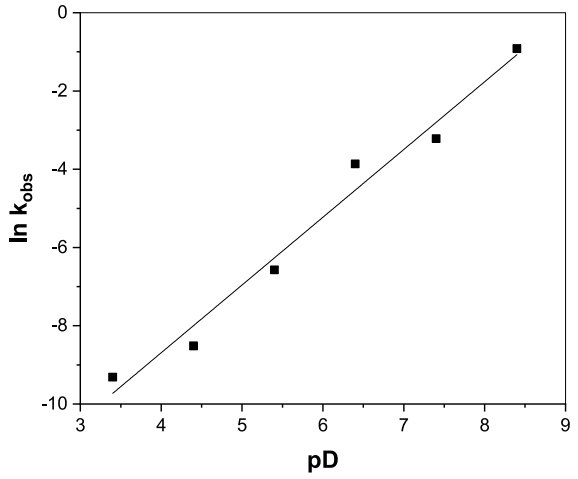

Figure 2. Effect of pD on the rate constant of Ce^{IV}K reduction in the presence of Cys.

Higher temperatures and ionic strength accelerated the Ce^{IV}K reduction in the presence of Cys. Kinetic measurements of the Ce^{IV}K/Cys redox reaction at temperatures between 25 and 50 °C showed that an increase in temperature leads to increase in k_{obs} (Figure 3 and Figure S1 and Table S3). Using

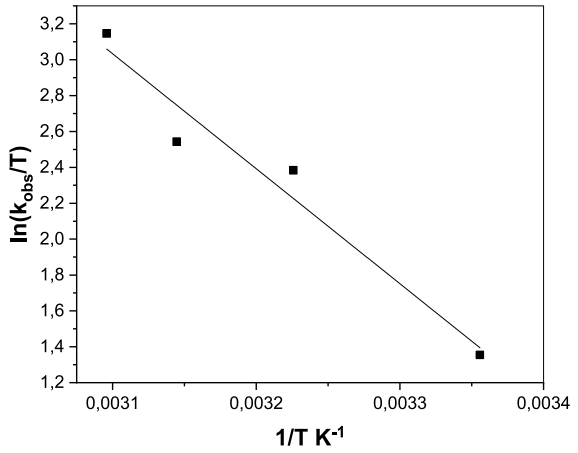

Figure 3. Eyring plot of $\ln(k_{obs}/T)$ as a function of $1/T$ (R^2 = 0.954) for the reduction of Ce^{IV}K in the presence of Cys.

these results, the activation parameters of the reaction were determined by plotting the data according to Arrhenius and Eyring equations. This resulted in E_a = 50.7 kJ mol^{-1}, $\Delta H^{\ddagger}$ = 53.3 kJ mol^{-1}, and $\Delta S^{\ddagger}$ = −7.1 J mol^{-1} K^{-1}, while the Gibbs free energy of activation at 60 °C was calculated to be 55.7 kJ mol^{-1}. The negative entropic value suggests a complex formation between Ce^{IV}K and Cys. Another indication of complex formation between Ce^{IV}K and Cys was the faster reduction of Ce^{IV}K observed upon increasing the ionic strength of the solution by adding 0.05 M $NaClO_4$. Increasing the ionic strength helps in shielding the electrostatic repulsion between the negatively charged carboxylate group of the Cys and POM surface, facilitating the reagent approximation interaction and thereby accelerating the reaction.[62,29,63,64]

Redox Activity of Ce^{IV}K toward Aromatic Amino Acids (Trp, Tyr, Phe, and His). In contrast to the fast reaction between Ce^{IV}K and Cys yielding Ce^{III}K and cystine, the reduction of Ce^{IV}K in the presence of the redox-active aromatic amino acids Trp, Tyr, Phe, and His was much slower, and no products of amino acid oxidation could be detected. When equimolar amounts of Trp or Tyr were mixed with Ce^{IV}K at pD 7.4 and room temperature, 14% and 7% reduction to Ce^{III}K was observed shortly after mixing, respectively. On the other hand, in the presence of His and Phe the reactivity was observed only after 7 days at pD 7.4 and 60 °C (Scheme 1). Further, although the Ce^{IV}K reduction was evident by ^{31}P NMR spectroscopy, no changes in the aromatic amino acid structures could be detected by ^{1}H NMR and ESI(+)/MS, suggesting that aromatic amino acids mediate the reduction of Ce^{IV}K to Ce^{III}K in a catalytic fashion. By changing the stoichiometry between Trp or Tyr and Ce^{IV}K, we confirmed the catalytic nature of this reduction, as complete reduction of Ce^{IV}K to Ce^{III}K occurred in the presence of 25 mol % of Trp, and partial reductions were detected with even lower Trp loadings (Figure 4 and Scheme S1). Given the precedents

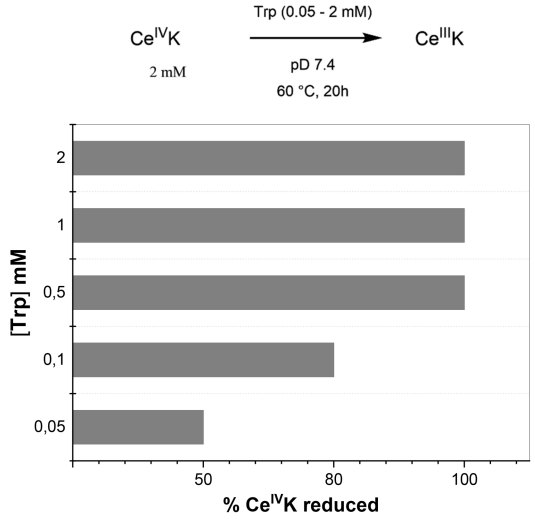

Figure 4. Reduction of Ce^{IV}K with different Trp concentrations. Reaction conditions: Ce^{IV}K (2 mM), amino acid (see chart), pD 7.4, 60 °C, 20 h (^{31}P NMR yield).

confirming the formation of a Trp radical upon reaction with Ce^{IV} salts using fast-flow electron spin resonance (ESR) spectroscopy[65] and resonance Raman spectroscopy,[66] it is very likely that this amino acid catalyzed reduction follows a radical pathway, and the medium of the reaction contributes to the fast regeneration of the amino acid structures.

Using Trp as a model substrate for the aromatic amino acids, kinetic measurements were performed to evaluate the effect of concentration, pD, temperature, and ionic strength in the reduction of Ce^{IV}K in the presence of aromatic amino acids. Overall, the redox reaction between Trp and Ce^{IV}K followed a first-order kinetic law with respect to Ce^{IV}K. Interestingly, the rate of reaction is largely affected by the pD value (Figure 5a). While at pD 3.4 no Ce^{IV}K reduction could be detected after 24 h, the reaction half-life ($t_{0.5}$) decreased dramatically from 165 h at pD 4.4 to only 2 h 40 min at pD 8.4 (Table S5). This faster

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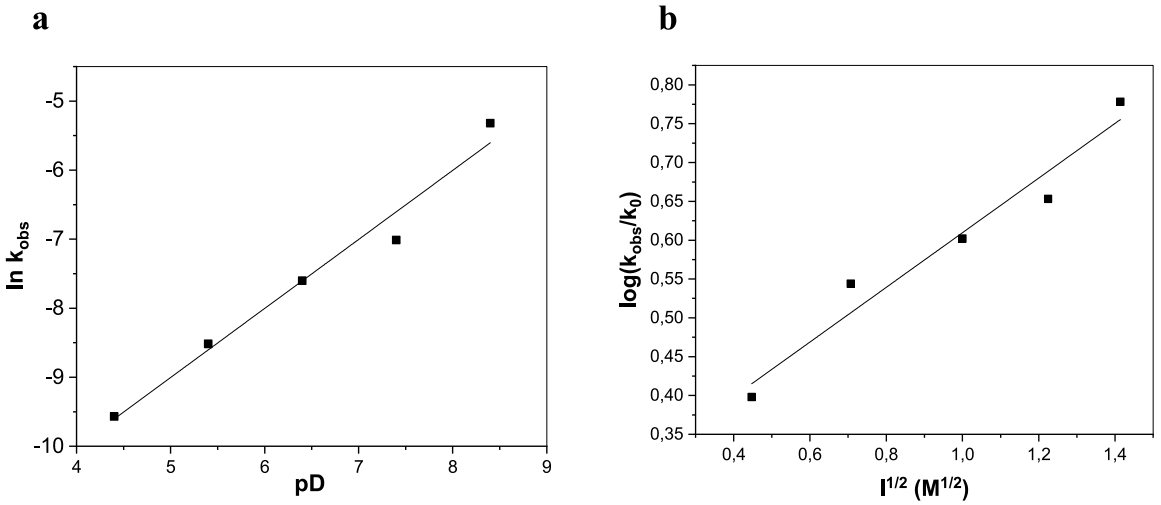

Figure 5. (a) pD dependence of the rate constant for the reduction of $Ce^{IV}K$ (2 mM) by 2 mM Trp at rt. (b) Influence of ionic strength on the rate constant of the reduction of $Ce^{IV}K$ (2 mM) in the presence of Trp (2 mM) at pD 6.4 and rt.

reduction is consistent with the decrease in redox potential of the Trp residue at higher pD values, strengthening the hypothesis of a Trp radical involvement in the reduction of Ce^{IV} to Ce^{III}.[47,46] Furthermore, when the reaction was carried out at temperatures ranging from 25 to 60 °C at pD 7.4, an increase in reaction rate upon an increase in temperature was observed (Figure S2), similarly to the reaction involving Cys. When the obtained data were plotted according to the Arrhenius and Eyring equations (Figure 6 and Figure S2),

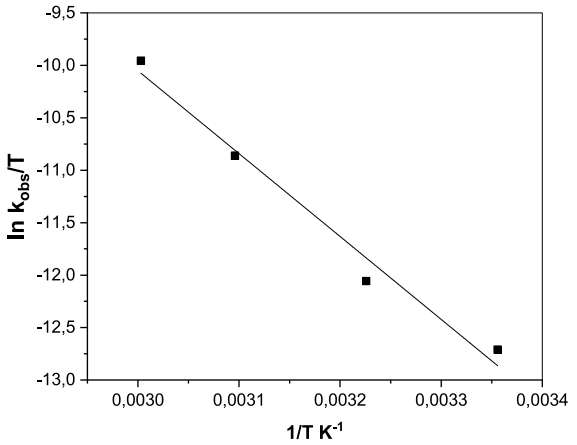

Figure 6. Eyring plot of $\ln(k_{obs}/T)$ as a function of $1/T$ (R^2 = 0.980) for the reduction of $Ce^{IV}K$ at pD 7.4 in the presence of Trp.

the activation energy was found to be 68.3 kJ mol^{-1}, while the $\Delta H^{\ddagger}$ = 65.7 kJ mol^{-1} and $\Delta S^{\ddagger}$ = −83.9 J mol^{-1} K^{-1} (Table S7). Finally, the addition of different concentrations of $NaClO_4$ (0.2−2 M) at pD 6.2 and 25 °C led to an increase in the $Ce^{IV}K$ rate of reduction (Figure 5b), which could be rationalized as discussed above for Cys. A similar reaction behavior was observed for the reduction of $Ce^{IV}K$ in the presence of Tyr (see the Supporting Information for details).

Redox Activity of Peptides. In addition to the amino acids, the redox activity of $Ce^{IV}K$ in the presence of peptides containing Trp, Tyr, and Cys redox-active amino acids was also probed. Solutions containing equimolar amounts (2 mM) of $Ce^{IV}K$ and peptide at pD 7.4 and room temperature (rt) were prepared, and the kinetics of the redox reactions were studied. As expected, the presence of peptides led to the reduction of $Ce^{IV}K$ to $Ce^{III}K$, but the estimated rate constants and half-lives were rather distinct from those of the isolated amino acids (Table 1). While $Ce^{IV}K$ reduction was slower in the presence

Table 1. Observed Rate Constants (k_{obs}) and Half-Lives ($t_{0.5}$, min) for the Reduction of $Ce^{IV}K$ in the Presence of "Redox Active" Amino Acids and Their Related Peptides

$K_{10}[Ce^{IV}(PW_{11}O_{39})_2]$ —(Peptide; pD 7.4, r.t.; 1day)→ $K_{11}[Ce^{III}(PW_{11}O_{39})_2]$

$Ce^{IV}K$ → $Ce^{III}K$

amino acid	k_{obs}	$t_{0.5}$	peptide	k_{obs}	$t_{0.5}$
Cys	35[a]	13	GSH	0.9[a]	570
Tyr	1[a]	580	Gly-Tyr	5.6[a]	145
Trp	0.9[b]	968	Gly-Trp	0.8[b]	1008

[a]In units of 10^{-3} mM^{-1} min^{-1}. [b]In units of 10^{-3} min^{-1}.

of γ-Glu-Cys-Gly (glutathione, GSH) than in the presence of Cys, Gly-Tyr provided a faster reaction rate than Tyr, and no differences were detected between Trp amino acid and Gly-Trp dipeptide. These behaviors are consistent with a previous report in which the incorporation of Tyr into small peptides lowered its redox potential, leading to a more favorable oxidation, while that for Trp showed no significant difference, especially if it was placed in the C-terminal position.[47] Similarly, Cys has a redox potential lower than that of GSH and the observed rate of $Ce^{IV}K$ reduction in the presence of GSH was approximately 1 order of magnitude slower in comparison to that of Cys. This could be attributed not only to the lower redox potential of Cys in comparison to GSH, which makes it more likely to be oxidized,[45,44] but also to the fact that the larger size of GSH in comparison to Cys might cause steric hindrance that affects its interaction with the $Ce^{IV}K$. Analogous to the reactions with isolated amino acids, the formation of a disulfide bridge was detected upon GSH oxidation (Figure S6), while products resulting from Gly-Tyr and Gly-Trp dipeptides were not observed. Interestingly, no hydrolysis of peptides was detected, indicating that the redox reactions are much faster than the hydrolytic cleavage. Furthermore, the redox reactions

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Inorg. Chem. XXXX, XXX, XXX−XXX

result in the formation of the hydrolytically inactive $Ce^{III}K$, due to the weaker Lewis acidity of Ce^{III} in comparison to Ce^{IV}.[5]

Tuning the Redox Behavior of Ce^{IV} Ions. The loss of active catalyst through reduction of $Ce^{IV}K$ to $Ce^{III}K$ motivated us to attempt a further tuning of the redox activity through exchange of the POM scaffold, as the Ce-POM redox potential has been reported to depend on (i) POM charge and (ii) the flexibility of POM ligand.[67] For instance, complexation of cerium ion to a Keggin or Wells−Dawson (WD) polyoxotungstate anion (Figure 7) leads to a decrease in its redox

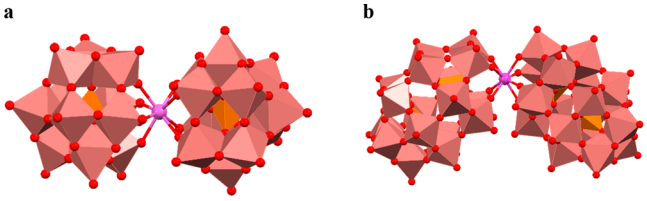

Figure 7. Difference in structures between (a) $Ce^{IV}K$, $[Ce^{IV}(PW_{11}O_{39})_2]^{10-}$ and (b) $Ce^{IV}WD$, $[Ce^{IV}(\alpha_2\text{-}P_2W_{17}O_{61})_2]^{16-}$. The $Ce^{IV/III}$ metal is represented by a purple ball. W groups are represented by brown octahedra, oxygen is represented by red balls, and the internal PO_4 groups are represented by gold tetrahedra.

potential from +1.44 V vs NHE to +0.88 and +0.78 V vs NHE, respectively (Table S11).[59,68] Strikingly, the small 0.10 V difference in the redox potential of $Ce^{IV}K$ and $Ce^{IV}WD$ resulted in a large difference in the rate of the redox reaction for both Cys and aromatic amino acids. The reduction of $Ce^{IV}K$ was at least 1 order of magnitude faster in comparison to $Ce^{IV}WD$ (Table 2), in accordance with the higher redox potential of $Ce^{IV}K$ in comparison to $Ce^{IV}WD$. In addition to the redox potential, other factors such as the different charges and steric hindrances of $Ce^{IV}K$ and $Ce^{IV}WD$ may also account for the observed difference in reactivity.

Table 2. Rate Constants and $t_{0.5}$ Values for the Reduction of 2 mM $Ce^{IV}K$/WD with 2 mM Amino Acids at pD 7.4 and Room Temperature

	$Ce^{IV}K$		$Ce^{IV}WD$	
amino acid	k_{obs}	$t_{0.5}$ (h)	k_{obs}	$t_{0.5}$ (day)
Cys	35[a]	1	0.2[a]	5.5
Tyr	1[a]	29	0.07[a]	19
Trp	0.9[b]	13	0.05[b]	9.5

[a]In units of 10^{-3} mM^{-1} min^{-1}. [b]In units of 10^{-3} min^{-1}.

Interactions of $Ce^{IV}K$ with Amino Acids and Peptides. The reduction of $Ce^{IV}K$ to $Ce^{III}K$ observed in the presence of amino acids suggests that they interact in solution. These interactions were investigated using NMR spectroscopy[69] to follow the changes in ^1H and/or ^{13}C NMR chemical shifts ($\Delta\delta$) of amino acids in the presence of $Ce^{IV/III}K$. Generally, only small changes were observed in the ^1H NMR spectra of amino acids in the presence of $Ce^{IV}K$, while ^{13}C NMR spectra provided more information regarding the possible mode of interaction, although multiple variables may affect the binding and consequently the chemical shifts, such as the dynamic nature of the complex formed between different amino acids and Ce^{IV}-POMs, the presence of radical species, and the presence of the paramagnetic $Ce^{III}K$ complex.

Cysteine and GSH. ^1H and ^{13}C NMR chemical shift values of Cys (Table S12) indicate its coordination with Ce^{IV} ion, most likely via O or/and N atoms, consistent with the low affinity of Ce^{IV} toward soft S ligands due to its intrinsic hardness.[70] The interactions between GSH and $Ce^{IV}K$ were also examined via ^1H and ^{13}C NMR spectroscopy (Table S15). Consistently, the large $\Delta\delta$ values detected at the C-terminus (C8 and C9) and at the carbonyl group (C5) of the γ-Glu-Cys amide linkage pointed to GSH complexation to $Ce^{IV}K$ via the carbonyl group close to the S−H moiety, probably playing a key role in positioning the reactive thiol group to the electron transfer step. These results imply that the coordination modes have an influence on the redox reaction kinetics, since it is well-known that the distance between the electron donor and acceptor plays a crucial role in the electron transfer step.[71,72] This could also explain the different reactivities of Cys and GSH. The distance between $Ce^{IV}K$ and the Cys thiol group is shorter when $Ce^{IV}K$ is complexed to Cys than when it is complexed to GSH, where the peptide coordination to $Ce^{IV}K$ also happens via the terminal carboxylate group of the Gly residue. The presence of two coordination modes in the GSH−$Ce^{IV}K$ complex would require a reorganization prior to the electron transfer step, thus slowing the redox reaction.

Aromatic Amino Acids. The ^{13}C NMR spectroscopy of a $Ce^{IV}K$ and Trp equimolar mixture showed only small changes in chemical shift values, indicating that the interactions between Trp and $Ce^{IV}K$ are likely electrostatic in nature. The planar and rather bulky nature of the tryptophan indole ring might prevent an effective interaction between the Ce ions and the carboxylate group. In addition, a repulsion between the negatively charged POM surface and the π cloud of aromatic groups could also prevent the direct coordination of NH_3^+ and COO^- groups of Trp to Ce^{IV} metal. However, the slightly higher ^{13}C chemical shift value detected for C2 could be an indication for an interaction occurring at the N indole atom, most likely in the form of a hydrogen bond between NH indole and a POM surface oxygen.[73−75] To further probe the electrostatic component of the interactions and its effect on the redox reaction, we carried out control experiments using N-, O-, and N,O-protected tryptophan derivatives (YHN-Trp-COX), so that amino or carboxylate groups were blocked. ^{31}P NMR spectroscopy indicated that a very low percentage (16%) of $Ce^{IV}K$ was reduced when it was incubated with Boc-Trp-OMe at 60 °C for 2 days, while incubation with H-Trp-OMe or Boc-Trp-OH resulted in 86% and 99% reduction of $Ce^{IV}K$, respectively (Figure S5). It is worth noting that the reaction mixtures were homogeneous at 60 °C. These results indicate that even ^{13}C NMR spectroscopy indicated a weak interaction between $Ce^{IV}K$ and amino and carboxylate groups of Trp; these groups are essential for the reaction between $Ce^{IV}K$ and amino acids and for the subsequent reduction of $Ce^{IV}K$ to $Ce^{III}K$. These results could also indicate that H-bonding interactions might play a key role in this reactivity.

CONCLUSION

In summary, a detailed account of the redox behavior of Ce^{IV}-POMs toward amino acids and peptides has been described. The reduction of Ce^{IV}-POMs to Ce^{III}-POMs was observed in the presence of cysteine and aromatic amino acids (relative rates: Cys ≫ Trp > Tyr > Phe ≈ His). Interestingly, only Cys afforded a new product (cystine), while no oxidation products were detected for the aromatic amino acids, suggesting that the reaction medium plays a role in the reaction mechanism. In all cases, an increase in pD, temperature, and ionic strength resulted in a faster redox reaction. Moreover, the incorporation

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Inorg. Chem. XXXX, XXX, XXX−XXX

of redox-active amino acids into peptides led to changes in the redox reaction kinetics but provided a similar reactivity pattern. It is worth noting that no hydrolysis of peptides was observed, indicating the redox reaction is favored over the hydrolytic pathway. Changing the POM scaffold from Keggin to Wells–Dawson largely inhibited the reduction of the Ce^{IV} center, showcasing the potential to tune Ce^{IV} redox activity and opening a fertile niche to explore both the redox and Lewis acidic activity of Ce^{IV}-POMs. Finally, amino acids and peptides interacted with the Ce^{IV}-POM mainly through direct coordination to the Ce ion, electrostatic interactions, and/or hydrogen bonding depending on the nature of the amino acid. In general, free carboxylate and amino groups of the amino acids were crucial for an effective reduction of Ce^{IV}-POM. Together, these results provide important insights into the redox activity of Ce-POMs toward amino acids and peptides. Further studies to tune this redox activity and further develop Ce-POMs potential as artificial proteases are ongoing in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.inorgchem.0c00993.

$Ce^{IV}K$ reduction by different amino acids, rate constants of $Ce^{IV}K$ reduction by Trp, Tyr, and Cys under different conditions, Arrhenius and Eyring plots for Cys oxidation by $Ce^{IV}K$ and $Ce^{IV}K$ reduction by Trp and Tyr, activation parameters of Cys oxidation and $Ce^{IV}K$ reduction by Trp and Tyr, redox potentials of $Ce^{IV}K$ and $Ce^{IV}WD$, ^{1}H and ^{13}C NMR spectroscopy chemical shift values of amino acids and peptides in the presence and absence of $Ce^{IV/III}K$, ^{1}H NMR spectra of GSH in the presence and absence of $Ce^{IV}K$, ^{31}P NMR spectra for the interaction between $Ce^{IV}K$ and protected Trp derivatives (YHN-Trp-COX) (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Tatjana N. Parac-Vogt − *KU Leuven, Department of Chemistry, 3001 Leuven, Belgium;* orcid.org/0000-0002-6188-3957; Email: tatjana.vogt@kuleuven.be

Authors

Shorok A. M. Abdelhameed − *KU Leuven, Department of Chemistry, 3001 Leuven, Belgium*

Laurens Vandebroek − *KU Leuven, Department of Chemistry, 3001 Leuven, Belgium*

Francisco de Azambuja − *KU Leuven, Department of Chemistry, 3001 Leuven, Belgium*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.inorgchem.0c00993

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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