Enhanced Oxidation of Tetracycline by Permanganate via the Alkali-Induced Alteration of the Highest Occupied Molecular Orbital and the Electrostatic Potential

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Supporting Information

ABSTRACT: The reaction between tetracycline and alkaline permanganate was investigated by combining experimental and computational methods. The kinetics was initially studied using a stopped-flow technique and was found to be first-order in tetracycline and permanganate. The second-order rate constant was positive linearly dependent on the concentration of hydroxyl ion (0.01–0.10 M), indicating the presence of base catalysis. By construction of the Eyring plots in the range of 293–308 K, a lower activation barrier ((14.89 ± 0.44) kcal mol⁻¹) was obtained at 298 K for the base-catalyzed pathway compared with that ((17.72 ± 1.84) kcal mol⁻¹) for the uncatalyzed pathway. The effect of ionic strength further suggested the existence of a complex with higher charge and reactivity. It is confirmed by the theoretical analysis that the hydroxyl ion could attract the proton of tetracycline toward itself to form a complex-like structure with a highly reactive phenolate-type moiety. The highest occupied molecular orbital of tetracycline was then transformed from double bond to aromatic ring. The result is supported by the product analysis that the initial oxidation of tetracycline by permanganate occurred predominantly at phenolic group in an alkaline aqueous solution. The base-catalyzed effect was finally explained by electrostatic potential that hydroxyl ion was able to increase the negative charge of tetracycline, making its phenolic group a more electron-rich moiety for electrophilic attack.

1. INTRODUCTION

Antibiotics were invented to protect people from bacterial infection, but now they have gained increasing attention as an emerging class of environmental pollutants. Tetracycline (TC), one of the most commonly used antibiotics, is employed worldwide in human therapy for controlling diseases and in livestock production for promoting growth.^{1,2} It is reported that the annual consumption of TC has reached more than 5900 tons in the U.S., 2300 tons in Europe, and 9400 tons in China.^{3–5} Due to the high consumption, TC was regularly detected in numerous environmental media including soil, groundwater, surface water, and municipal wastewater.^{6–9} This has inevitably raised the public concern because the long-term exposure to TC may induce the development of antibiotic resistant bacteria and antibiotic resistant genes, which subsequently threatens ecological environment and human health.¹⁰ Consequently, it is of great importance to develop an efficient technology for TC degradation during water treatment.

As a high-valent metal-oxo species, permanganate anion (MnO₄⁻) is one of the most versatile and powerful oxidants, widely used in chemistry for applications such as inducing chemiluminescence, preparing functional substances, and establishing chemical oscillation.^{11–13} It is cheap, stable, and also fairly effective against the various emerging pollutants such as phenolic compounds, endocrine disrupting chemicals and antibiotics.^{14–17} In recent years, research on MnO₄⁻ has undergone a significant development. The concerted mechanism was recognized to be applicable for the MnO₄⁻ oxidation of alkanes and alkenes.^{18–21} The in situ formed manganese species was explored to enhance the transformation of phenolic compounds by MnO₄⁻.^{14,15} However, as a very fundamental issue, the role of hydroxyl ion (OH⁻) in the base-catalyzed

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MnO_4^- oxidation remains unclear. Only few studies have speculated that OH^- could, for instance, complex with MnO_4^- or with the unsaturated bond to form highly reactive intermediates.^{22–25}

Owing to both practical and theoretical importance, the TC oxidation by aqueous alkaline MnO_4^- was examined in this work by combining experimental and computational methods. The reaction kinetics was first determined by a stopped-flow spectrophotometer that allows a continuous monitoring of the fast reaction.²⁶ The studies on the reactivity were performed by varying the reaction conditions such as reactant concentration, temperature (T), and ionic strength (I). The kinetic and thermodynamic results were then obtained to elucidate the reaction mechanism. Additionally, the density functional theory (DFT) calculation, which has been proved to be a critical approach in the mechanistic study of chemical reactions, was adopted here to clarify the role of OH^- in TC oxidation by MnO_4^- .^{19–21,27,28} The quantum structures and the corresponding wave functions were supported by the product analysis data and were further used to explain the outcome of kinetic investigation.

2. EXPERIMENTAL SECTION

2.1. Chemicals and Materials. Sodium perchlorate (NaClO_4), sodium hydroxide (NaOH), potassium permanganate (KMnO_4), and formic acid were at least of analytical grade and purchased from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China). TC with purity of 96% was obtained from Jing Ke Hong Da Biotechnology Co., Ltd. (Beijing, China). Acetonitrile at HPLC grade was applied as solvent from Thermo Fisher Scientific (USA). The water used throughout the experiments was purified by a Millipore Milli-Q unit to a final resistivity of $\geq 18.2 \text{ M}\Omega \text{ cm}$. All working solutions were prepared daily and stored in the dark. NaOH was employed to provide the required alkalinity and in combination with NaClO_4 to maintain the desired I .

2.2. Kinetic Studies. An Applied Photophysics stopped-flow spectrophotometer (model SX20, Leatherhead, U.K.) was used to perform the kinetic experiments. Temperature was controlled in the range of 293–308 K by using an automatic water circulator (Thermo Fisher Scientific, Waltham, MA) connected to the stopped-flow's sample handling unit. The TC concentration was kept in at least 10-fold excess of that of KMnO_4 to maintain the pseudo-first-order condition. For each kinetic run, the reaction was initiated by simultaneously injecting an equal volume of TC and KMnO_4 solutions into the optical cell of the stopped-flow. The decay of MnO_4^- , as denoted by the 525 nm absorption peak, was continuously monitored. According to the previous study,²³ kinetic traces were analyzed by using the single exponential equation (Pro-Data software, Applied Photophysics Ltd.):

$$\text{Abs}_t = (\text{Abs}_0 - \text{Abs}_\infty) \exp(-k_{\text{obs}}t) + \text{Abs}_\infty \quad (1)$$

where k_{obs} represents the pseudo-first-order rate constant; Abs_0 , Abs_t , and Abs_∞ are the absorbances at time 0, t , and infinity, respectively. Unless otherwise stated, the reported data points represent the mean of three independent experiments. The standard deviations were usually within 5% and thus were not given in this work.

2.3. Product Studies. The product analysis of the TC oxidation by KMnO_4 in alkaline medium ($[\text{OH}^-] = 0.10 \text{ M}$) were implemented at different molar ratios of KMnO_4 to TC. After disappearance of the green color, which indicates the characteristic absorption of manganate at 610 nm, the reaction

solution was filtered and analyzed by a Waters HPLC system equipped with a Micromass Q-TOF mass spectrometer. Separation was performed on an Agilent C18 column (150 mm $\times$ 4.6 mm, 3.5 μm) at a flow rate of 0.2 mL min^{-1} with two mobile phases consisting of A (0.1% formic acid in water) and B (acetonitrile). The gradient elution was 0–3 min, 95% A and 5% B; 3–10 min, a linear gradient to 85% A and 15% B; 10–25 min, 85% A and 15% B; 25–30 min, a linear gradient to 75% A and 25% B; 30–35 min, 75% A and 25% B; 35–40 min, a linear gradient to 60% A and 40% B; 40–45 min, 60% A and 40% B; 45–50 min, a linear gradient to 95% A and 5% B; 50–60 min, 95% A and 5% B. The ESI-MS analysis was carried out under the positive electrospray ionization mode with a full scan mass range of $m/z = 50$ –1000. The drying gas was nitrogen at 10 L min^{-1} at 200 $^\circ\text{C}$, and the capillary voltage was 3.5 kV.

2.4. Computational Studies. The density functional theory (DFT) calculations were conducted with Gaussian 09 software.²⁹ The B3LYP model together with LanL2DZ basis set for the manganese atom and 6-31+G(d) basis set for other atoms was employed throughout this work. The solvent effects in water were taken into account by means of the IEFPCM model. The geometries of all species were fully optimized, and then the vibrational frequencies were calculated for all optimized structures to confirm the nature of the stationary points. The wave function analysis was also implemented in the Gaussian 09 program. The three-dimensional diagrams of optimized structure, the highest occupied molecular orbital (HOMO), and the electrostatic potential were constructed with Gaussview.

2.5. Kinetic Salt Effect. According to the literature,³⁰ the reaction scheme of a simple bimolecular reaction can be written as

where X and Y represent the reactants; C^{++} represents the transition state; P represents the product; K is the thermodynamic equilibrium constant; and k^{++} is the reaction rate constant. Thus, the reaction rate can be expressed as

$$\frac{d[\text{P}]}{dt} = k^{++}[\text{C}^{++}] \quad (3)$$

By considering the thermodynamic equilibrium

$$K = \frac{[\text{C}^{++}]}{[\text{X}][\text{Y}]} \frac{\gamma_{\text{C}^{++}}}{\gamma_{\text{X}}\gamma_{\text{Y}}} \quad (4)$$

where γ_{X} , γ_{Y} , and $\gamma_{\text{C}^{++}}$ are the activity coefficients of the relative species, eq 3 can be rewritten as

$$\frac{d[\text{P}]}{dt} = k^{++}K[\text{X}][\text{Y}] \frac{\gamma_{\text{X}}\gamma_{\text{Y}}}{\gamma_{\text{C}^{++}}} = k[\text{X}][\text{Y}] \quad (5)$$

where k is the second-order rate constant determined experimentally and can be considered as a function of activity coefficients:

$$k = k^{++}K \frac{\gamma_{\text{X}}\gamma_{\text{Y}}}{\gamma_{\text{C}^{++}}} \quad (6)$$

For an aqueous solution with I below 0.50 M,³¹ the Davies equation can be used to calculate the value of the activity coefficient (γ):

$$\log \gamma = -Az^2 \left(\frac{\sqrt{I}}{1 + \sqrt{I}} - 0.3I \right) \quad (7)$$

where $A = 0.509$ for water at 298 K and z is the charge of the ion. Particularly for the transition state (C^{++}), the charge number should be the sum of z_A and z_B . On the basis of eq 7, the activity coefficient equals a value of 1 when I is zero. Equation 6 can be then rewritten as

$$k = k_0 \frac{\gamma_X \gamma_Y}{\gamma_{C^{++}}} \quad (8)$$

where k_0 (i.e., k^{++K}) is the second-order rate constant at $I = 0$. Substituting eq 7 into eq 8 gives

$$\log k = \log k_0 + 2Az_X z_Y \left(\frac{\sqrt{I}}{1 + \sqrt{I}} - 0.3I \right) \quad (9)$$

Equation 9 presents the kinetic salt effect in this work and was utilized to study the effect of I on k .

3. RESULTS AND DISCUSSIONS

3.1. Reaction Kinetics. **3.1.1. Reaction Order.** As shown in Figure 1, the reaction progress of TC oxidation by MnO_4^- was

Figure 1. Spectral changes at 0.1 s time intervals in the oxidation of TC (0.50 mM) by MnO_4^- (0.05 mM) with $[OH^-] = 0.10$ M and $I = 0.11$ M at 298 K. Inset: the corresponding kinetic trace at wavelength 525 nm ($Abs_0 = 0.12$ and $Abs_f = 0.04$).

monitored by a stopped-flow spectrophotometer under pseudo-first-order condition (10-fold excess of TC) with fixed $[OH^-]$ and I . The reduction of MnO_4^- could be readily identified by the distinct absorbance peak at 525 nm, which was accompanied by an increase of a band with maximum at 610 nm due to the formed manganate. The inset of Figure 1 shows the decay of MnO_4^- at 525 nm, which could be fitted well to a single exponential curve as described by eq 1. A plot of the pseudo-first-order rate constant k_{obs} versus $[TC]$ yields a straight line with a zero intercept (Figure S1 in Supporting Information). These results suggest that the reaction is of first-order with respect to each reactant and second-order in total. Thus, the second-order rate constant k could be obtained by dividing k_{obs} by $[TC]$.

3.1.2. Effect of $[OH^-]$. The variation in the values of k was then studied with different $[OH^-]$ (0.01–0.10 M). Figure 2a shows the linear correlation between k and $[OH^-]$ in the range from 293 to 308 K. Similar alkali-dependent behavior was also observed for the reaction of MnO_4^- with other species.^{24,32} The results suggest the following rate law:

$$-\frac{d[MnO_4^-]}{dt} = (k_1 + k_2[OH^-])[MnO_4^-][TC] \quad (10)$$

where k_1 and k_2 are the rate constants of the uncatalyzed and base-catalyzed reaction pathways, which can be obtained from the intercepts and slopes of the plots of k versus $[OH^-]$.

Figure 2. (a) Plots of k versus $[OH^-]$ with $I = 0.11$ M at 293 K (blue), 298 K (red), 303 K (green), and 308 K (pink); (b) Eyring plots constructed using k_1 (blue) and k_2 (red) with $I = 0.11$ M; (c) effects of I on k with $[OH^-] = 0.01$ M (blue) and $[OH^-] = 0.10$ M (red) at 298 K in the oxidation of TC (0.50 mM) by MnO_4^- (0.05 mM). The fit parameters for the linear correlations are given in Table S1.

3.1.3. Effect of Temperature. The thermodynamic parameters were further analyzed by constructing the Eyring plots for k_1 and k_2 as shown in Figure 2b. The enthalpy (ΔH^{++}) and entropy (ΔS^{++}) of activation were found to be (11.63 ± 0.92) kcal mol $^{-1}$ and $-(20.43 \pm 3.08)$ cal K $^{-1}$ mol $^{-1}$ for the uncatalyzed reaction pathway and (2.84 ± 0.22) kcal mol $^{-1}$ and $-(40.45 \pm 0.73)$ cal K $^{-1}$ mol $^{-1}$ for the base-catalyzed reaction pathway. The corresponding free energies of activation (ΔG^{++}) for the uncatalyzed and base-catalyzed reaction pathways were then determined at 298 K to be (17.72 ± 1.84) and (14.89 ± 0.44) kcal mol $^{-1}$, respectively. The lower activation barrier for the base-catalyzed reaction pathway may explain the enhanced reactivity of TC with MnO_4^- in the case of higher $[OH^-]$. In addition, the more negative value of ΔS^{++} also implies the existence of a more unstable transition state for the base-catalyzed process.

3.1.4. Effect of Ionic Strength. The influence of I on k was studied with $[OH^-] = 0.01$ and 0.10 M at 298 K. In both conditions, the experimental data in Figure 2c could be fitted well to eq 9, which was a modification of the Debye–Hückel model suitable for $I < 0.50$ M. The observed slope ($z_X z_Y$) of (2.67 ± 0.14) at $[OH^-] = 0.01$ M is consistent with a bimolecular reaction between MnO_4^- and doubly deprotonated TC (TC^{2-}), which comprised more than 99.8% of TC above pH 12 (Figure S2). However, the slope ($z_X z_Y$) of (5.68 ± 0.35) at $[OH^-] = 0.10$ M is so large as to suggest the presence of an ion with higher charge. This result also corresponds to the increased

contribution of the base-catalyzed reaction pathway to k accompanying the increment of $[\text{OH}^-]$ (Table S2). In particular, the major reaction pathway at $[\text{OH}^-] = 0.10 \text{ M}$ was the base-catalyzed oxidation of TC by MnO_4^- , with the contribution equaling 92.4%. Therefore, it is reasonable to infer that OH^- might combine with MnO_4^- and/or TC^{2-} to form a complex with higher charge and reactivity.

3.2. Reaction Mechanism. **3.2.1. Product Analysis.** Prior to inquiry of the mechanism of TC oxidation by alkaline MnO_4^- , the potential product was analyzed based on liquid chromatography–mass spectrometry. The same method has been successfully implemented to characterize the degradation products and to propose the plausible mechanism in the treatment of TC.^{33–35} It should be noted here that though the applied oxidants were variable, the initial reaction sites were always identified to be the phenolic, olefinic, and dimethylamino groups. These are exactly the electron-rich moieties susceptible to electrophilic attack by permanganate.^{14–17} However, in contrast to the previous works, one main product was present accompanied by the abatement of TC in this work as shown in Figure 3. The molecular ion peak was observed at $m/z = 459$,

Figure 3. (a) LC–MS chromatograms at different ratios of MnO_4^- versus TC; (b) MS spectrum of the major transformation product quinone-substituted TC (QSTC, either ortho or para).

which is in agreement with the characteristic product (ortho or para quinone-substituted TC, QSTC) usually found for TC degradation.^{34,35} The corresponding reaction mechanism should be similar to that described in literature. It is proposed to involve an initial attack of phenolic group on the TC, yielding a precursor diphenol structure with a molecular weight increase of 16 Da (the equivalent of one oxygen atom). The diphenol structure could go through further hydrogen abstraction to afford QSTC with an overall mass gain of 14 Da compared to TC. It is thus reasonable to suggest that the rate-limiting step of TC oxidation by alkaline MnO_4^- occurred predominantly toward the TC's phenolic group under the OH^- -controlled condition.

3.2.2. Quantum Structure Analysis. On the basis of the kinetic and product analysis, structures of the highly reactive species were proposed as below. The preliminary combination of MnO_4^- and OH^- was then assumed to occur in alkaline medium to give a hydroxylated species $[\text{MnO}_4\text{OH}]^{2-}$, which would

subsequently decompose to generate MnO_4^{2-} and hydroxyl radical ($\cdot\text{OH}$).^{22,36} This could explain some literature reports but is not applicable here based on the following facts: first, TC should participate in the rate-limiting step of our reaction in view of the first-order dependence on $[\text{TC}]$; second, the reaction rate constant ($6.3 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$) of TC with $\cdot\text{OH}$ is so much larger than the k values (10^3 – $10^4 \text{ M}^{-1} \text{ s}^{-1}$) observed in this study.³³ Hence, $[\text{MnO}_4\text{OH}]^{2-}$ instead of $\cdot\text{OH}$ was suggested to be a potential oxidant accelerating the reactions.^{16,23} Then we attempted to locate $[\text{MnO}_4\text{OH}]^{2-}$ by performing DFT calculations on the basis of the hypothesized structure.³⁷ Figure 4a shows the representative steps of the geometry optimization

Figure 4. Snapshots of attempted optimizations of the proposed complex: (a) $[\text{MnO}_4\text{OH}]^{2-}$; (b) $[\text{TCOH}]^{3-}$; (c) $[\text{TC}(\text{OH})_2]^{4-}$.

of $[\text{MnO}_4\text{OH}]^{2-}$. The proposed complex dissociated rapidly with an energy decrement of $87.85 \text{ kcal mol}^{-1}$ and finally converged on a hydrogen bond complex (step 66), indicating no existence of $[\text{MnO}_4\text{OH}]^{2-}$ in the reaction.

Formation of a complex between TC^{2-} and OH^- was proposed to be an alternative mechanism for the base-catalyzed MnO_4^- oxidation. In light of the previous studies, OH^- was assumed to be added to the unsaturated bond and/or to be

coordinated to hydrogen atom.^{24,25} Both could produce more electron-rich species with higher charge. It is also worth noting that the previous similar mechanisms usually have a reaction order of unity on OH^- , which is consistent with the data obtained in this work. Therefore, by considering the result of product analysis, we tried to add OH^- to the ortho and para positions of the phenolic moiety of TC in DFT calculations. This seems plausible because the aromatic ring has an unsaturated structure and is exactly the site of initial attack by MnO_4^- . However, all attempts resulted in the immediate departure of OH^- from TC and failed to find a stable stationary point (data not shown).

In contrast, the addition of OH^- to the vicinity of the phenolic hydroxyl group could successfully produce an optimized structure of $[\text{TCOH}]^{3-}$ (Figure 4b), in which the proton migrated to OH^- . This is reasonable because there is a large amount of OH^- around the TC molecule in an alkaline medium. An analogous result ($[\text{TC}(\text{OH})_2]^{4-}$) could also be obtained by adding a second OH^- , as can be seen in Figure 4c. No previous study has reported the possible deprotonation of TC^{2-} in this pH range ($[\text{OH}^-] = 0.01\text{--}0.10\text{ M}$). Hence, we proposed that OH^- could just attract the proton to form a complex-like structure with TC^{2-} . The resulting phenolate-type moiety should be more reactive with MnO_4^- than the phenol moiety of TC^{2-} .³⁸

3.2.3. Quantum Wave Function Analysis. To gain a deeper insight into the mechanism, the HOMOs of the proposed structures were plotted as shown in Figure 5a. It is well

rich region being susceptible to electrophilic attack. As can be seen in Figure 5b, the negative charge on the surfaces of both $[\text{TCOH}]^{3-}$ and $[\text{TC}(\text{OH})_2]^{4-}$ were greatly increased in comparison to that of TC^{2-} . While the OH^- was merely located at the vicinity of phenolic hydroxyl group, the increased negative charge was dispersed to a much larger area, thus promoting the reactivity of TC for MnO_4^- oxidation at the ortho and para positions of the phenolic moiety.

4. CONCLUSIONS

We performed experimental and computational experiments to investigate MnO_4^- oxidation of TC in alkaline aqueous solution. The reaction was found to be overall second-order with first-order with respect to each reactant. Linear alkali-dependent behavior of k was observed in the range of 293–308 K, indicating the involvement of both uncatalyzed and base-catalyzed pathways. A lower activation barrier was then obtained to explain the higher reaction rate for the base-catalyzed pathway. The results on the effect of I further suggested that OH^- tended to combine with MnO_4^- and/or TC^{2-} to form a complex with higher charge and reactivity. It is confirmed by the DFT calculations that OH^- could attract the proton toward itself to form a complex-like structure with TC^{2-} , resulting in a highly reactive phenolate-type moiety. On the basis of the proposed structures, HOMO of TC was found to be transformed from double bond to aromatic ring, which was exactly the predominant reaction site clearly demonstrated by the product analysis. The base-catalyzed effect was finally disclosed by electrostatic potential that OH^- was able to increase the negative charge of TC, making the phenolic group a more electron-rich moiety for electrophilic attack.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.iecr.7b00288.

Plot k_{obs} vs $[\text{TC}]$, speciation diagram of TC, fit parameters, and contributions reaction pathways to k in TC oxidation (PDF)

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The authors declare no competing financial interest.

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Figure 5. Plots of (a) the HOMO (isovalue = 0.05) and (b) the electrostatic potential (isovalue = 0.001) for the proposed structures of TC^{2-} , $[\text{TCOH}]^{3-}$, and $[\text{TC}(\text{OH})_2]^{4-}$.

established that the frontier orbital theory has been proved as a reliable tool to understand the chemical reactivity.^{39,40} On addition of OH^- , the HOMOs of both $[\text{TCOH}]^{3-}$ and $[\text{TC}(\text{OH})_2]^{4-}$ were apt to be localized on the aromatic ring instead of the double bond in TC^{2-} . The result is consistent with that obtained from the product analysis and thus suggests that participation of OH^- could alter the regioselectivity of the reaction. The acceleration effect of OH^- was further studied by calculating the electrostatic potential of the proposed structures. It has been demonstrated that electrostatic potential is recognized as an effective technique for interpreting and predicting the reactive behavior of molecules.^{41,42} The more negative electrostatic potential usually means the more electron-

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