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Mechanistic Investigation of Substrate Oxidation by Ce(IV) Reagents in Acetonitrile

Yang Zhang and Robert A. Flowers, II*

Department of Chemistry and Biochemistry, Texas Tech University, Box 41061, Lubbock, Texas 79409-1061

robert.flowers@ttu.edu

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Abstract: Rates and activation parameters for the Ce^{4+}-mediated oxidation of a β-keto ester, a β-diketone, and a β-keto silyl enol ether were determined in acetonitrile. In the case of the dicarbonyls, the enol content of the substrate impacts the rate of oxidation by Ce^{4+}, predominantly through contributions from $\Delta H^{\ddagger}$. For the silyl enol ether, the transition state for oxidation by Ce^{4+} is substantially more ordered than it is for the β-keto ester or the β-diketone.

Compounds based on Ce(IV) represent some of the most utilized oxidants in organic synthesis, and the common reagent ceric ammonium nitrate (CAN) has been used for a wide variety of organic transformations including the oxidation of aromatic substrates,[1] olefins,[2] alcohols,[3] hydroquinones,[4] carbonyls,[5] and other functional groups.[6] Although CAN is the most utilized Ce(IV)-based reagent, others have been developed including cerium(IV) acetate,[7] cerium(IV) trifluoroacetate,[8] cerium(IV) methanesulfonate,[9] and cerium(IV) trifluoromethanesulfonate.[1b] Although much of the early work with Ce(IV) reagents was carried out in strongly acidic media, more recently mild protocols have been developed in traditional organic solvents such as acetonitrile and methanol. While Ce(IV) oxidants have been used with success in various reactions, very little work has been performed to compare and contrast the reactivity of different Ce(IV)-based reagents.

Aside from functional group oxidation, Ce(IV) reagents have been used to carry out oxidative bond-forming reactions as well.[10] Ce(IV)-mediated oxidative additions of silyl enol ethers and diones to dienes,[11] activated alkenes,[12] and unactivated alkenes[13] proceed in good to excellent yields. The initial reactive intermediate generated in these reactions are radical cations. Until recently, radical cations were considered to be interesting but synthetically ineffectual intermediates. The work of Schmittel,[14] Crich,[15] Newcomb,[16] and others has certainly dispelled this notion. Radical cations have a number of intrinsic properties that make them important intermediates for organic transformations. Although there are numerous methods for generating radical cations, the use of cerium reagents has several advantages including relative abundance, ease of preparation, low cost, and low toxicity. During the past 10 years there has been an increased appreciation of the utility of Ce(IV) for generating radical cations that can react to form C−C bonds.[10,17]

While there are a number of advantages to using Ce(IV) reagents in synthesis, there are a number of problems as well. Many transformations require large quantities of Ce(IV) and side products resulting from internal ligand transfer are common. Although great strides have been made using Ce(IV)-mediated bond-forming conversions, there is little understanding of the discreet mechanistic details of these reactions. A better understanding of the mechanistic details of Ce(IV) oxidations will allow chemists to “fine tune” reaction conditions so that byproducts are eliminated and reactions can be carried out in an efficient manner.

Herein we present our initial thermochemical and mechanistic studies on CAN and ceric tetrabutylammonium nitrate (CTAN). The rates and activation parameters for the oxidation of methyl acetoacetate, 4-(trimethylsiloxy)-3-penten-2-one, and 1,3-cyclohexanedione by CAN and CTAN in acetonitrile are presented.

Experimental Section

Ceric tetrabutylammonium nitrate (CTAN) was prepared according to literature procedure.[18]

Electrochemistry. The redox potentials of CAN and CTAN in acetonitrile were measured by cyclic voltammetry. The working electrode was a standard glassy carbon electrode. The electrode was polished with 0.05 mm polishing alumina and

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TABLE 1. Rate Constants and Activation Parameters for the Oxidation of Methyl Acetoacetate, 1,3-Cyclohexanedione, and (Trimethylsiloxy)-3-penten-2-one by CAN and CTAN

oxidant-substrate system	k (mol^{-1} s^{-1})^{a,b}	E_a (kcal mol^{-1})^c	$\Delta S^\ddagger$ (cal mol^{-1}, K^{-1})^d	$\Delta H^\ddagger$ (kcal mol^{-1})^d	$\Delta G^\ddagger$ (kcal mol^{-1})^e
CAN−methyl acetoacetate	$1.5 \pm 0.1 \times 10^{-1}$	22 ± 1	8 ± 2	22 ± 1	19 ± 2
CTAN−methyl acetoacetate	$3.9 \pm 0.4 \times 10^{-2}$	23 ± 2	9 ± 2	23 ± 2	20 ± 2
CAN−1,3-cyclohexanedione	$1.1 \pm 0.1 \times 10^{2}$	18 ± 1	5 ± 2	17 ± 1	16 ± 2
CTAN−1,3-cyclohexanedione	$4.7 \pm 0.5 \times 10^{1}$	20 ± 1	9 ± 2	19 ± 1	16 ± 1
CAN−(trimethylsiloxy)−3-penten-2-one	$1.2 \pm 0.1 \times 10^{2}$	10.6 ± 0.8	-20 ± 1	10.0 ± 0.8	16 ± 1
CTAN−(trimethylsiloxy)−3-penten-2-one	$5.3 \pm 0.2 \times 10^{1}$	12.2 ± 0.6	-17 ± 1	11.6 ± 0.6	16.7 ± 0.5

[a] All rate data are the average of at least two independent runs. [b] Experimental uncertainties were propagated through these calculations, and all values are reported as $\pm\sigma$. [c] Calculated from $E_a = \Delta H^\ddagger + RT$. [d] Eyring activation parameters were obtained from $\ln(k_{obs}h/kT) = -\Delta H^\ddagger/RT + \Delta S^\ddagger/R$. [e] Calculated from $\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$.

cleaned in an ultrasonic bath. The electrode was rinsed with acetone or ethanol and dried before each run. The auxiliary electrode was a platinum wire. A saturated Ag/AgNO$_3$ electrode was used as the reference. The electrolyte employed in all experiments was tetrabutylammonium hexafluorophosphate, lithium nitrate, or tetrabutylammonium nitrate. The concentration of CAN or CTAN in all of the electrochemical experiments was 0.5 mM. All solutions were prepared in a drybox and transferred to the electrochemical analyzer for analysis.

Stopped-Flow Rate Studies. Kinetic experiments in acetonitrile were performed with a stopped-flow spectrophotometer. The Ce^{4+} oxidant and substrates were taken separately in airtight syringes from a glovebox and injected in to the stopped-flow system. The cellblock and the drive syringes of the stopped flow reaction analyzer were flushed at least three times with dry degassed acetonitrile to make the system anaerobic. The concentration of Ce^{4+} used for the study was 2.5 mM. The concentration of substrates was kept high relative to [Ce^{4+}] (0.025 to 0.25 M) in order to maintain pseudo-first-order conditions. Reaction rates were determined from the decay of the Ce^{4+} absorbance at 330 nm. The decay of Ce^{4+} displayed first-order behavior over >4 half-lives for all Ce^{4+}−substrate combinations. The temperature studies were carried out over a range between 10 and 40 °C using a refrigerated circulator connecting to the sample-handling unit of the stopped-flow reaction analyzer. The step size used for the temperature study was 5 °C, and each kinetic trace was recorded at a known temperature that was measured by a thermocouple in the reaction cell.

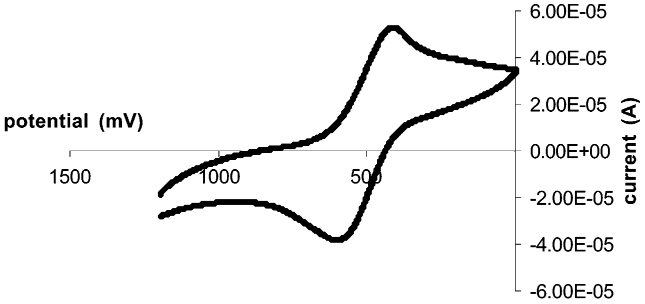

FIGURE 1. Cyclic voltammogram of CAN at glassy carbon electrode in acetonitrile vs Ag/AgNO$_3$ reference electrode.

Results and Discussion

Initial experiments involved determining the relative oxidizing power of CAN and CTAN. There are a number of difficulties with the electrochemical analysis of lanthanides. The main difficulty is that lanthanides tend to coordinate the negative counterions of many common electrolytes so electrochemical measurements will provide potentials for the coordinated lanthanide complex, which is not the redox potential of interest. We have examined numerous electrolytes and determined their effect on the UV−vis spectrum of CAN and CTAN in acetonitrile. Tetraalkylammonium electrolytes containing perchlorate or tetrafluoroborate counterions tended to coordinate to the Ce. After examining numerous electrolytes, it was found that tetrabutylammonium hexafluorophosphate, lithium nitrate, and tetrabutylammonium nitrate were reasonable electrolytes for CAN and CTAN. These electrolytes did not change the color of either oxidant and inspection of the UV−vis spectra of either reagent containing these electrolytes displayed no changes of the peaks contained in the UV or visible region. Figure 1 contains a cyclic voltammogram of CAN in acetonitrile using lithium nitrate as the electrolyte and a saturated Ag/AgNO$_3$ electrode. The $E_{1/2}$ value of CAN was found to be 550 ± 10 mV while the $E_{1/2}$ value of CTAN was determined to be 540 ± 10 mV. As expected, the redox potentials for both oxidants were the same (within experimental error), indicating that changing the counterion from ammonium to tetrabutylammonium has no effect on the thermodynamic oxidizing power of the Ce^{4+} ion.

The next goal was to determine the rates of oxidation of a β-keto ester, a β-diketone, and a β-keto silyl enol ether, three common substrates utilized in Ce^{4+} oxidations. The pseudo-first-order rate constants for the oxidation of both substrates display a first-order dependence on [Ce^{4+}] and on [substrate]. The data are consistent with the rate law shown in eq 1.

$$\text{rate} = k[\text{Ce}^{4+}][\text{substrate}] \tag{1}$$

The rate constants and activation parameters for the oxidation of methyl acetoacetate, 1,3-cyclohexanedione, and (trimethylsiloxy)-3-penten-2-one by CAN and CTAN are contained in Table 1. A representative stopped-flow kinetic trace is shown in Figure 2.

Examination of the rate constants in Table 1 clearly shows that the silyl enol ether and the 1,3-diketone are oxidized by Ce^{4+} at a significantly faster rate than the β-keto ester. Enols and enol ethers are known to be oxidized more readily than the corresponding β-dicarbonyls.[19] The enol content of methyl acetoacetate and 1,3-cyclohexanedione in acetonitrile are approximately 5% and 70%, respectively, as determined by ^{1}H NMR.[20] It is likely that the rate-limiting step of the oxidation of the β-ketoester is the tautomeric enol content. Further

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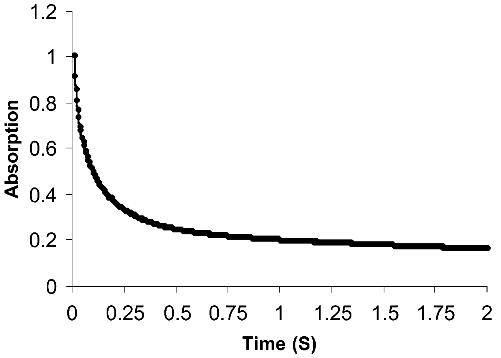

FIGURE 2. Stopped-flow trace showing the decay of CAN absorbance at 330 nm in the presence of (trimethylsiloxy)-3-penten-2-one at 25 °C.

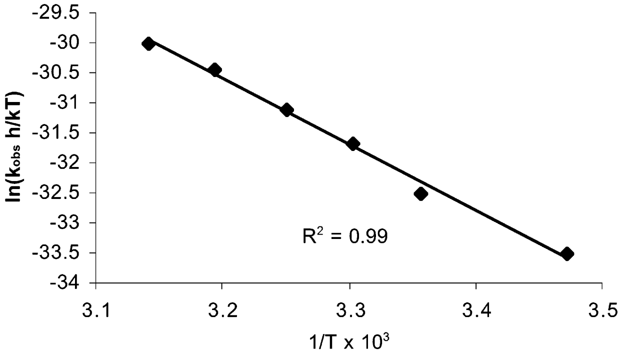

FIGURE 3. Eyring plot for CAN/methyl acetoacetate system.

mechanistic studies will determine whether this supposition is correct.

Interestingly, the rates of oxidation of substrates by CAN and CTAN are different even though their thermodynamic redox potentials are the same. The bimolecular rate constants for the oxidation of all substrates by CAN are approximately 2 to 3 times faster than oxidation by CTAN. This finding suggests the relatively large tetrabutylammonium counterion of CTAN may be associated with the cerium complex to some extent, thus altering the oxidation of substrates through steric interactions.

Next, rates were measured over a 30 degree temperature range to obtain activation enthalpies and entropies from the linear form of the Eyring eq 2. Figure 3 contains a representative Eyring plot.

$$\ln(k_{\mathrm{obs}}h/kT) = -\Delta H^{\ddagger}/RT + \Delta S^{\ddagger}/R \qquad (2)$$

The activation parameters (Table 1) for the oxidation of the silyl enol ether and the 1,3-dicarbonyls by both Ce^{4+} reagents show some interesting differences. While care must be taken in comparing and evaluating the activation data for CAN and CTAN since they are within experimental error of each other, a general trend is present. For each substrate, E_a, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$ are slightly higher for CTAN than CAN. The slightly higher barrier and subsequent decrease in order is consistent with the tetrabutylammonium ion of CTAN playing a modest role in the oxidations.

Comparison of the activation parameters for the β-dicarbonyl substrates shows some interesting differences as well. Although there is a 1000-fold difference in the bimolecular rate constants for the Ce^{4+}-mediated oxidation of methyl acetoacetate and 1,3-cyclohexanedione, the $\Delta S^{\ddagger}$ values are the same within experimental error. Comparison of $\Delta H^{\ddagger}$ for the oxidation of methyl acetoacetate and 1,3-cyclohexanedione by either Ce reagent shows that the energy required for bond reorganization in the transition state is 4−5 kcal/mol lower in the latter case. The $\Delta H^{\ddagger}$ values parallel the reaction rates and indicate that the oxidation of β-dicarbonyls by Ce^{4+} is enthalpically driven (at least for these two cases).

In contrast to β-dicarbonyls, oxidation of (trimethylsiloxy)-3-penten-2-one by either Ce^{4+} reagent have relatively large negative entropies of activation and low barriers for $\Delta H^{\ddagger}$. Even though the rates of oxidation of 1,3-cyclohexanedione and (trimethylsiloxy)-3-penten-2-one (hence the $\Delta G^{\ddagger}$ values) are the same within experimental error, the activated complex for the oxidations are significantly different. The silyl enol ether oxidation proceeds through a more ordered transition state, and the energy required for bond reorganization is substantially lower than that of the diketone.

Conclusions

The data in this series of experiments shows that small changes in oxidant or substrate structure can have an impact on the mechanism of oxidation. In the case of β-dicarbonyls, the enol content of the substrate impacts the rate of oxidation by Ce^{4+}, predominantly through contributions from $\Delta H^{\ddagger}$. For the β-ketosilyl enol ether substrate studied here, the transition state for oxidation by Ce reagents is substantially more ordered than it is for the β-dicarbonyls examined in this study. Finally, replacement of the ammonium cation of CAN with tetrabutylammonium has a modest impact on the rate of oxidation of all substrates examined in this study. We are currently carrying out a systematic mechanistic and thermochemical study of the role of solvents and ligands on the thermodynamic redox potential of Ce(IV) reagents and the role of solvent milieu on substrate oxidation. The results of these experiments will be published in a forthcoming series of papers.

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Supporting Information Available: General methods, decay traces, plots of rate data, and electrochemical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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