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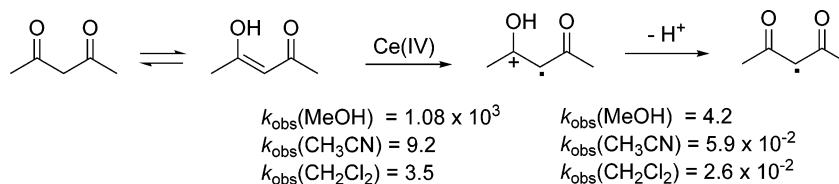
Mechanistic Studies of Ce(IV)-Mediated Oxidation of β-Dicarbonyls: Solvent-Dependent Behavior of Radical Cation Intermediates

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$k_{obs}(MeOH) = 1.08 \times 10^3$ $k_{obs}(MeOH) = 4.2$
$k_{obs}(CH_3CN) = 9.2$ $k_{obs}(CH_3CN) = 5.9 \times 10^{-2}$
$k_{obs}(CH_2Cl_2) = 3.5$ $k_{obs}(CH_2Cl_2) = 2.6 \times 10^{-2}$

The Ce(IV)-initiated oxidation of synthetically relevant β-diketones and β-keto silyl enol ethers was explored in three solvents: acetonitrile, methylene chloride, and methanol. The studies presented herein show that the rate of reaction between Ce(IV) and the substrates is dependent upon the polarity of the solvent. Thermochemical studies and analysis are interpreted to be consistent with transition state stabilization by solvent being primarily responsible for the rate of substrate oxidation. Kinetic investigation of radical cations obtained from oxidations of β-diketones reveals that a more ordered transition state for the radical cation decay is achieved through the direct involvement of methanol in the deprotonation of the intermediate. In the case of radical cations derived from β-keto silyl enol ethers, experimental data support a mechanism involving unimolecular decay of the intermediate. Remarkably, radical cations derived from β-diketones and β-keto silyl enol ethers are surprisingly stable in methylene chloride.

Introduction

During the past two decades, there has been an increasing acceptance of single electron transfer (SET) oxidation as a means to promote bond-forming reactions in organic synthesis.[1–3] During the SET oxidation of a neutral organic substrate, a radical cation is formed and the seminal work of a range of chemists[4–8] has shown that the intrinsic properties of these intermediates can be used to drive an array of important bond-forming reactions. Several methods can be employed to generate radical cations, including anodic oxidation of electron-rich olefins, photochemical excitation of a neutral substrate, and SET oxidation of a neutral species initiated by a chemical oxidant.[4a] In the latter context, reagents based on Ce(IV) (most notably ceric ammonium nitrate (CAN)) have emerged as valuable SET oxidants for a variety of reactions due to their relative abundance, ease of preparation, low cost, and low toxicity.

Oxidations utilizing CAN and other Ce(IV)-based reagents have been used to carry out a number of bond-forming

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reactions.[9] Ce(IV)-mediated oxidative additions of silyl enol ethers and diones to dienes,[10] activated alkenes,[11] and unactivated alkenes[12] proceed in good to excellent yields. More recently, intramolecular versions of the aforementioned reactions including the oxidative addition of silyl enol ethers[13] and β-diketones[14] to olefins have been developed as well. While the usefulness of radical cation intermediates generated through Ce(IV)-initiated oxidation in organic synthesis is recognized, there are potential drawbacks as well. During the oxidation of organic substrates, the initial formation of a radical cation is usually followed by rearrangement or follow-up reactions that lead to free radical intermediates. Typically, the free radical reacts with another substrate (olefin, etc.) to form a new C−C bond and a product radical. Oxidation of the free radical intermediate to a cation leads to capture of solvent or nitrate expelled from CAN upon its reduction to Ce(III) and these alternative mechanistic pathways result in many of the side products prevalent in oxidations. Therefore, preparative Ce(IV) initiated oxidations cannot be achieved in many instances. Chemical intuition suggests that these pathways can be depressed by understanding the interrelationship between the mechanism of oxidation by Ce(IV), the effect of solvent on the stability of the initially formed radical cation intermediate, and the rates (mechanisms) of the various available pathways.

Previous studies have shown that the oxidation of enols and their structurally related silyl enol ethers generate radical cations[10] which undergo deprotonation by solvent assistance to generate the corresponding radicals.[15] Although these studies provide an important mechanistic framework for understanding the interrelationship between the solvent milieu, the stability of the radical cation, and follow-up reactions with solvent or substrate, many of these studies utilized sterically hindered starting materials whose structures are not representative of substrates used in organic synthesis. The goal of the present work was to examine the solvent dependence of the rate of oxidation of commonly utilized β-diketones and their related β-keto silyl enol ethers by Ce(IV) reagents. The surprising stability of radical cations derived through these oxidations also allowed us to assess the role of solvent on the mechanism of decay of the reactive intermediates.

Results and Discussion

Rate of Oxidation of β-Diketones and Related Substrates. The influence of solvent on the rate of oxidation of a series of β-diketones (**1**−**3** and **5**) and two β-keto silyl enol ethers (**4** and **6**) by CAN or Ceric tetra-*n*-butylammonium nitrate (CTAN) was examined by using stopped-flow spectrophotometry and the rate of reaction was monitored through the decay of the

Ce(IV) maximum absorbance at 330 nm. The structures of the substrates are contained in Table 1. All reactions provided carboxylic acids in CH$_3$CN and CH$_2$Cl$_2$ as previously reported.[16] Oxidation of **1** in CH$_3$OH provided 1-acetyl-2-tetralone as the major product[17] whereas all other oxidations provided methyl esters as the major products.[16]

Recent work in our group has revealed that while CTAN oxidizes substrates more slowly than CAN by a factor of 2, they behave in a mechanistically analogous manner.[18] Since CTAN and CAN are soluble in CH$_3$CN, the rates were compared in the same solvent for three β-diketones and two β-keto silyl enol ethers to compare both the impact of the bulky tetra-*n*-butylammonium countercation and solvent on oxidation rates. All oxidations were carried out under pseudo-first-order conditions employing concentrations 1 mM of Ce(IV) and 20 mM of substrate. The data for the observed rate constants obtained by monitoring the decay of the Ce(IV) absorption are contained in Table 1. In all cases, the rates display a first-order dependence on [Ce(IV)] and [substrate] consistent with the rate law shown in eq 1.

$$\text{rate} = k[\text{Ce(IV)}][\text{substrate}] \tag{1}$$

During the course of synthetic studies, the orange color of the Ce(IV) ion was found to disappear rapidly upon addition of substrate and a subsequent appearance of a persistent red color was observed in the solutions that faded with time. To examine this in detail, time-resolved absorption spectra were obtained with use of stopped-flow spectrophotometry. Figure 1 contains the time-resolved absorption spectrum for the oxidation of **1** by CAN in CH$_3$CN at room temperature. An isosbestic point was observed at 400 nm, which indicates that an intermediate is formed in solution. Closer inspection of Figure 1 shows the growth of an absorption between 430 and 480 nm, with a maximum at 460 nm. Since no absorption was observed for CAN, β-diketones, or the Ce(III) reaction product beyond 400 nm (Supporting Information), the absorption at 460 nm was interpreted to be the formation of the radical cation of **1**. This observation is consistent with the fact that many radical cations have an absorption in the range of 400 to 500 nm.[19] The inset in Figure 1 shows a closer view of the growth of the radical cation with time. A very similar time-resolved absorption spectrum was obtained for the oxidation of **1** by CTAN in CH$_2$Cl$_2$ at room temperature (Supporting Information). Oxidation of other β-diketones shows similar time-resolved spectra in the different solvents. It is worth noting that this is the first time that radical cations from such simple substrates have been observed spectroscopically under standard laboratory conditions. With these data in hand, the rate of the increase in absorption at 460 nm was monitored as a function of time and the subsequent decay of the radical cation was monitored as well. These data are also contained in Table 1.

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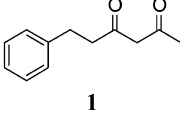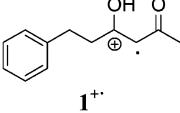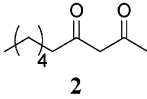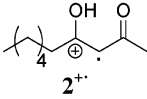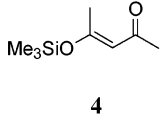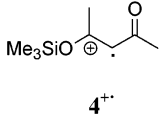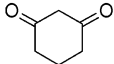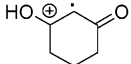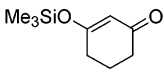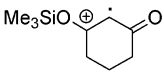
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TABLE 1. Observed Rate Constants for the Oxidation of 1,3-Diketones and Two Related β-Keto Silyl Enol Ethers by CAN in CH₃OH or CH₃CN and CTAN in CH₂Cl₂ or CH₃CN

| substrate	intermediate	oxidant and solvent	rate constant of Ce(IV) decay at 330 nm k_1 (sec^{-1})$^{a-c}$	rate constant of radical cation formation at 460 nm k_1' (sec^{-1})$^{a-c}$	rate constant of radical cation decay at 460 nm k_2 (sec^{-1})$^{a-c}$
1	**1⁺·**	CAN+ CH₃OH	$9.5\pm0.6 \times 10^2$	$9.7\pm0.5 \times 10^2$	3.3 ± 0.3
		CAN+CH₃CN	10.4 ± 0.1	10.8 ± 0.1	$9.8\pm0.4 \times 10^{-2}$
		CTAN+CH₃CN	8.3 ± 0.2	8.6 ± 0.2	$9.1\pm0.6 \times 10^{-2}$
		CTAN+CH₂Cl₂	3.5 ± 0.1	3.6 ± 0.1	$1.1\pm0.1 \times 10^{-2}$
2	**2⁺·**	CAN+ CH₃OH	$9.2\pm0.7 \times 10^2$	$9.5\pm0.3 \times 10^2$	2.7 ± 0.2
		CAN+CH₃CN	9.1 ± 0.9	8.9 ± 0.1	$1.8\pm0.2 \times 10^{-1}$
		CTAN+CH₂Cl₂	3.04 ± 0.30	3.32 ± 0.02	$3.6\pm0.3 \times 10^{-2}$
3	**3⁺·**	CAN+ CH₃OH	$1.07\pm0.04 \times 10^3$	$1.04\pm0.03 \times 10^3$	4.2 ± 0.2
		CAN+CH₃CN	9.2 ± 0.2	9.4 ± 0.1	$5.9\pm0.2 \times 10^{-2}$
		CTAN+CH₃CN	6.0 ± 0.2	5.9 ± 0.1	$5.5\pm0.2 \times 10^{-2}$
		CTAN+CH₂Cl₂	3.5 ± 0.1	3.54 ± 0.03	$2.6\pm0.1 \times 10^{-2}$
4	**4⁺·**	CAN+ CH₃OH	$3.8\pm0.2 \times 10^2$	$3.9\pm0.3 \times 10^2$	$4.0\pm0.2 \times 10^{-1}$
		CAN+CH₃CN	9.5 ± 0.3	9.7 ± 0.1	$1.7\pm0.1 \times 10^{-2}$
		CTAN+CH₃CN	5.9 ± 0.3	6.4 ± 0.1	$1.6\pm0.1 \times 10^{-2}$
		CTAN+CH₂Cl₂	6.2 ± 0.2	6.7 ± 0.1	$3.7\pm0.1 \times 10^{-3}$
5	**5⁺·**	CAN+ CH₃OH	$1.3\pm0.1 \times 10^3$	$1.5\pm0.1 \times 10^3$	16.0 ± 0.1
		CAN+CH₃CN	47 ± 1	49 ± 4	$1.3\pm0.1 \times 10^{-1}$
		CTAN+CH₃CN	37 ± 1	39 ± 3	$1.2\pm0.1 \times 10^{-1}$
		CTAN+CH₂Cl₂	14 ± 1	15 ± 1	$1.1\pm0.1 \times 10^{-2}$
6	**6⁺·**	CAN+ CH₃OH	$6.8\pm0.4 \times 10^2$	$7.1\pm0.7 \times 10^2$	4.8 ± 0.1
		CAN+CH₃CN	53 ± 1	55 ± 3	$6.2\pm0.5 \times 10^{-2}$
		CTAN+CH₃CN	42 ± 2	43 ± 4	$5.9\pm0.3 \times 10^{-2}$
		CTAN+CH₂Cl₂	32 ± 1	34 ± 3	$9.5\pm0.7 \times 10^{-3}$

^{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} All rate studies were carried out at 25 °C, [substrate] = 20 mM, [Ce(IV)] = 1 mM.

Evaluation of the data clearly shows that the observed rate constants for Ce(IV) decay (k_1) at 330 nm are equivalent to the observed rate constants of the radical cation formation (k_1') at 460 nm within experimental error for all of the substrates and all oxidant/solvent combinations.

Further examination of the rate data in Table 1 shows a number of interesting trends. The rate constants for the oxidation of β-diketones by Ce(IV) (or conversely, the formation of the radical cations) are solvent dependent in the order of CH₃OH $\gg$ CH₃CN > CH₂Cl₂. Generally, the rate of oxidation in CH₃OH is 70−100 times faster than those in CH₃CN for all β-diketones. Comparison of the rate of substrate oxidation in CH₃CN shows that CTAN oxidizes β-diketones at a slower rate

than CAN. Evaluation of the rate of substrate oxidation by CTAN in CH₂Cl₂ and CH₃CN shows that the rate of oxidation is slower in CH₂Cl₂. Overall, oxidation in CH₂Cl₂ is approximately half of the rate in CH₃CN.

To further explore the role of solvent, the rates of oxidation of two β-keto silyl enol ethers **4** and **6** were studied. Examination of the data for the β-keto silyl enol ethers contained in Table 1 shows that the rate of oxidation by CAN is greater in CH₃OH than in CH₃CN. Use of CTAN in CH₃CN showed that this reagent oxidized the substrate more slowly than CAN, a finding analogous to observations made for the β-diketones. Oxidation of the substrate by CTAN in CH₂Cl₂ provided the same rate as the trials in CH₃CN within experimental error for
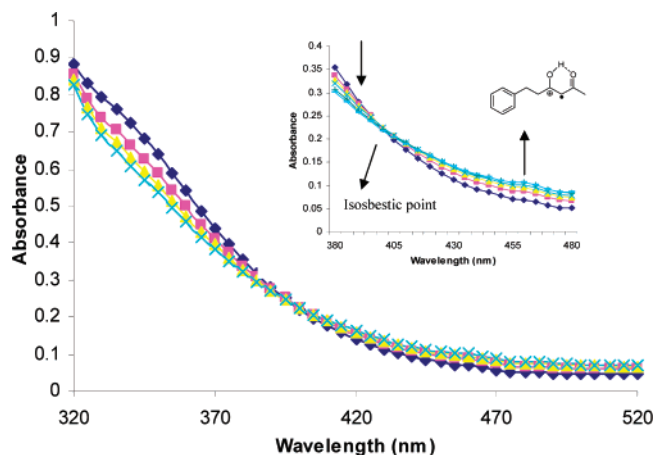
FIGURE 1. Time-resolved absorption spectrum observed from CAN and 6-phenyl-2,4-hexanedione in CH₃CN in the range of 320−520 nm ([diketone]:[CAN] = 20 mM:1 mM) at 25 °C. Inset: Wavelength range of 380−480 nm.

the silyl enol ether of 2,4-pentanedione **4** whereas the silyl enol ether of 1,3-cyclohexanedione **6** is slightly faster in CH₃CN than in CH₂Cl₂. Closer inspection of the data reveals other differences as well. The rates of oxidation of β-diketones are faster than their corresponding silyl enol ethers in CH₃OH while the rates of oxidation in CH₃CN are nearly the same within experimental error. In contrast, the rates of oxidation of the silyl enol ethers in CH₂Cl₂ are nearly double those observed for the β-diketones. Overall, these findings indicate that oxidation of the β-keto silyl enol ethers used in this study is less sensitive to solvent than structurally similar β-diketones.

While it is reasonable to expect that polar solvents will stabilize a charge-separated transition state and subsequently increase the rate of reaction, solvent can also affect the keto−enol tautomerism of β-diketones.[20] Enols and enol ethers are known to be oxidized more readily than the corresponding β-diketones.[4c] Since the enol content of β-diketones is solvent dependent, it is reasonable to expect that solvents promoting a high enol content should also lead to a greater rate of oxidation. The seminal study of Beak on the solvent-dependent enol content of β-diketones showed that in general, for keto−enol pairs in which the enol cannot form an internal hydrogen bond (such as **5** in this study), the equilibrium is predominantly controlled by the hydrogen-bonding basicity of the solvent, whereas for keto−enol pairs where intramolecular hydrogen bonding is possible (substrates **1−3** in this study), the polarity of the solvent plays a more important role in the equilibrium.[20] Results from the study of Beak show that the enol content of **3** follows the trend CH₂Cl₂ > CH₃OH > CH₃CN. Although **5** was not examined in this study, structurally similar 5,5-dimethylcyclohexane-1,3-dione was examined and the enol content followed the trend CH₃OH > CH₃CN > CH₂Cl₂. While the trend in the solvent-dependent enol content of **5** follows the rate of oxidation by Ce(IV) in these solvents, the rate of oxidation of **3** does not. Furthermore, the rates of oxidation of substrates **1−3** and **5** do not differ significantly in each solvent.

Another caveat with the present analysis is that the redox potentials of lanthanides are known to be sensitive to the solvent milieu.[21−23] As a result, it is possible that the solvent-dependent

oxidation rate could be due to the impact of solvent on the oxidizing power of Ce(IV) or the ease of oxidation of the substrate. To further clarify the role of solvent, the redox potentials of Ce(IV) were compared. Previous studies in our group have shown that changing the ammonium counterion to tetra-*n*-butylammonium has no impact (within experimental error) on the redox potential of Ce(IV), so the small differences in the rate of oxidation between CAN and CTAN are likely due to the steric bulk of the tetra-*n*-butylammonium counterion.[18] Cyclic voltammetry (CV) was utilized in a previous study to determine the redox potential of CTAN in CH₂Cl₂ and CH₃CN to establish whether solvent had a measureable impact on the ease of oxidation of Ce(IV). The measured potentials were 510 ± 20 and 540 ± 10 mV vs saturated Ag/AgNO₃. The redox potential of CTAN in CH₂Cl₂ was lower by 30 mV.[24] To determine the effect of CH₃OH on the redox potential of Ce(IV), CV experiments were carried out under identical conditions to those utilized previously. The $E_{1/2}$ of CAN in MeOH was determined to be 570 ± 20 mV vs saturated Ag/AgNO₃ (Supporting Information). These results show that Ce(IV) becomes a slightly better oxidant as the solvent polarity is increased, but the differences are small (60 mV through the range of solvents).

Unfortunately, attempts to measure the redox potentials of β-diketones and β-keto silyl enol ethers used in this study were unsuccessful as they provided irreproducible results. Previous studies by Schmittel have shown that there are only small differences (60 mV) in the oxidation potential for silyl enol ethers in CH₃CN and CH₂Cl₂ and that related enol ethers are only marginally easier to oxidize.[25] For example, the oxidation potentials of 1-(*tert*-butyldimethylsiloxy)-2,2-dimesityl-1-phenylethene vs the ferrocene/ferrocenium couple were found to be 0.73 and 0.67 V in CH₃CN and CH₂Cl₂, respectively, whereas the oxidation potential of 2,2-dimesityl-1-phenylethenol in CH₃CN was 0.61 V. On the basis of this analysis and the study of solvent on the redox potential of Ce(IV), it is unlikely that solvent has a major impact on the thermodynamic ease of substrate oxidation by CAN or CTAN. The lack of consistent trends among the solvent-dependent enol content of β-diketones **1−3** and **5** and the rate of oxidation suggest that the rate of oxidation may be due to transition state stabilization by a more polar solvent. This is supported by results with silyl enol ethers **4** and **6** (where enol content is not a consideration) displaying solvent-dependent oxidation trends similar to those of structurally related β-diketones. The somewhat decreased sensitivity of the silyl enol ethers to solvent may be due to the relatively large trimethylsilyl group, which leads to steric interactions between oxidant and the substrate.

Role of Solvent in Radical Cation Stability. Examination of the observed rate constants of radical cation decay (k_2) contained in Table 1 reveals a marked solvent dependence in every case in the order CH₃OH > CH₃CN > CH₂Cl₂. Typically, the k_2 in CH₃OH is 10−100 times greater than that in CH₃CN and the k_2 value in CH₃CN is 5−10 times larger than that in CH₂Cl₂. The decay rates (k_2) of radical cations **1⁺•**, **2⁺•**, and

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TABLE 2. Observed Rate Constants for the Decay of the Radical Cation of 3,3-Dideuterio-2,4-pentanedione in MeOH, CH₃CN, and CH₂Cl₂

entry	oxidant and solvent	k_D (s^{-1})$^{a-c}$	k_H/k_D
1	CAN+ CH₃OH	2.8 ± 0.1	1.50 ± 0.06
2	CAN+CH₃CN	$(2.7 \pm 0.1) \times 10^{-2}$	2.19 ± 0.05
3	CTAN+CH₂Cl₂	$(1.2 \pm 0.1) \times 10^{-2}$	2.17 ± 0.09

^{a} Observed rate constant for decay of the radical cation of 3,3-dideuterio-2,4-pentanedione. 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} All rate studies were carried out at 25 °C, [substrate] = 20 mM, [Ce(IV)] = 1 mM.

$\mathbf{3^{+\bullet}}$ in methanol are within experimental error indicating that intramolecular cyclization of $\mathbf{1^{+\bullet}}$ in this solvent occurs after the rate-limiting step of the reaction. Comparison of k_1, k_1', and k_2 shows that the decay of radical cations is the rate-determining step in all solvents. To further test this supposition, deuterium-labeled 3,3,-dideuterio-2,4-pentanedione was prepared and the observed rate constants of its radical cation decay were measured under identical conditions to those described previously. The data are summarized in Table 2. These experiments show that a primary isotope effect (k_H/k_D) of approximately 2 was observed in CH₃CN and CH₂Cl₂ whereas a k_H/k_D of 1.5 was found in CH₃OH. A similar primary kinetic isotope effect ($k_H/k_D = 2.7 \pm 0.5$) has been reported by Schmittel for the deprotonation of the anisyldimesitylethenol radical cation.[15a] The lower value in methanol is likely due to exchange between CH₃OH and deuterium in the substrate.

The deuterium isotope study coupled with the observation that more polar solvents lead to faster decay of a radical cation are consistent with the known solvent-assistant mechanism of O−H bond cleavage.[26,27] Comparison of k_2 for radical cations derived from oxidation of 2,4-pentanedione, 1,3-cyclohexanedione, and their structurally related silyl enol ethers shows that the presence of the silyl group stabilizes the radical cation intermediate in each solvent. These observations further support the role of solvent in the reaction of radical cations through O−H and O−Si cleavage since the larger trimethylsilyl group would be expected to react more slowly through a solvent-assisted O−Si bond cleavage mechanism.[25a]

To obtain more information on the behavior of radical cations in the different solvents, the activation parameters for the decay of radical cations at 460 nm were determined under pseudo-first-order conditions. The results and comparison with different radical cations, solvent, and Ce(IV) reagents are given in Table 3. Inspection of the activation data in Table 3 shows that changing the structure of β-diketones while keeping other conditions constant does not change the activation parameters greatly in this reaction system. Further evaluation of the activation parameters of the 6-phenyl-2,4-hexanedione radical cation, $\mathbf{1^{+\bullet}}$, and the 2,4-pentanedione radical cation, $\mathbf{3^{+\bullet}}$, decay demonstrates that there is a greater contribution from $\Delta H^{\ddagger}$ than $-T\Delta S^{\ddagger}$ to $\Delta G^{\ddagger}$ in acetonitrile and dichloromethane. Conversely, $-T\Delta S^{\ddagger}$ provides a greater contribution than $\Delta H^{\ddagger}$ to $\Delta G^{\ddagger}$ in methanol. For instance, $\Delta H^{\ddagger}$ for the decay of $\mathbf{1^{+\bullet}}$ in acetonitrile is 17 kcal mol^{-1}, accounting for 89% of $\Delta G^{\ddagger}$ (19 kcal mol^{-1}), while $-T\Delta S^{\ddagger}$ only accounts for 11% of $\Delta G^{\ddagger}$. By comparison, $\Delta H^{\ddagger}$ for the decay of $\mathbf{1^{+\bullet}}$ in methanol is 5.0 kcal mol^{-1},

accounting for 27% of $\Delta G^{\ddagger}$ (18.4 kcal mol^{-1}), whereas $-T\Delta S^{\ddagger}$ accounts for 73% of $\Delta G^{\ddagger}$.

Comparison of the role of solvent in the decay of the radical cation derived from a β-keto silyl enol ether, $\mathbf{4^{+\bullet}}$, with those derived from β-diketones shows that the decay is enthalpy driven in all solvents. As a consequence, a less ordered transition state was observed for $\mathbf{4^{+\bullet}}$ in the three solvents as well. These experimental observations are consistent with a higher energy barrier for O−Si bond cleavage than the O−H bond cleavage. Although the decay of $\mathbf{4^{+\bullet}}$ is enthalpy driven in all solvents, the order followed solvent polarity with $\Delta H^{\ddagger}$ having the lowest value in CH₃OH and the largest value in CH₂Cl₂.

The evidence described above suggests that the activated complexes for the decay of radical cations derived from β-diketones vary significantly in different solvents. The deprotonation of radical cations $\mathbf{1^{+\bullet}}$ and $\mathbf{3^{+\bullet}}$ in methanol proceed through a more ordered transition state and the energy required for bond reorganization and bond cleavage is substantially lower than that of less polar solvents (acetonitrile and methylene chloride). This is likely due to the direct involvement of CH₃OH in the deprotonation of $\mathbf{1^{+\bullet}}$ and $\mathbf{3^{+\bullet}}$. In the case of radical cation $\mathbf{4^{+\bullet}}$, the decay is enthalpy driven in all cases with $\Delta H^{\ddagger}$ showing an increase with decreasing solvent polarity.

All the kinetic data presented so far indicate CH₃OH may be intimately involved in the decay of radical cations as previously reported for other systems.[25a,28] To further investigate the role of CH₃OH in the decay of radical cations, the decay rates of $\mathbf{3^{+\bullet}}$ in the nonnucleophilic solvent CH₂Cl₂ were measured by using samples containing increasing amounts of CH₃OH. Figure 2 shows the plot with the rate constants of $\mathbf{3^{+\bullet}}$ decaying as a function of the concentration of CH₃OH. The plot in Figure 2 shows a linear relationship between the k_{obs} for $\mathbf{3^{+\bullet}}$ in CH₂Cl₂ and [CH₃OH]. On the basis of this analysis, the reaction order of CH₃OH was determined to be 0.94 ± 0.05 demonstrating that the decay is first order in CH₃OH and that solvent is intimately involved in the deprotonation of the radical cation and conversion to a radical intermediate. When experiments were carried out to determine the impact of [CH₃OH] on the decay of radical cation $\mathbf{4^{+\bullet}}$ in CH₂Cl₂, the reaction order of CH₃OH was found to be 0.24 ± 0.03 based on a plot of $\ln k_{obs}$ vs $\ln$[CH₃OH].

With these experiments in hand, it is instructive to place them in perspective with other mechanistic studies of radical cations. Kinetic studies of radical cations derived from a series of silyl enol ethers of 2,2-dimesityl-1-phenylethenol show that there is a strong solvent dependence on the rate of radical cation decay with an acceleration of $>10^3$ in CH₃CN vs CH₂Cl₂.[25a] Furthermore, nucleophiles present during the oxidation further enhanced the rates of radical cation decay. As a result, a nucleophile-assisted O−Si bond cleavage mechanism was proposed for the decay of this family of radical cations. In contrast, radical cations derived from enol acetates of 2,2-dimesityl-1-alkylethenol were shown to decay through a unimolecular pathway rather than a solvent-assisted mechanism.[27] In these studies, modest rate increases for the decay of radical cations on the order of 10- to 20-fold were observed in CH₃CN compared to CH₂Cl₂.
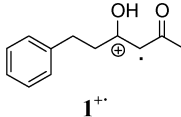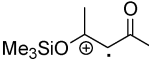
Previous studies taken together with the mechanistic data described herein support a mechanism where hydrogen bonding

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TABLE 3. Activation Parameters for the Decay of Selected Radical Cations[a−c]

radical cation	oxidant and solvent	$\Delta H^{\neq}$ (kcal mol^{-1})[d]	$\Delta G^{\neq}$ (kcal mol^{-1})[e]	$\Delta S^{\neq}$ (cal mol^{-1} K^{-1})[d]
1[+·]	CAN+ CH$_3$OH	5.0 ± 0.4	18.4 ± 0.7	-45 ± 1
	CAN+CH$_3$CN	17 ± 1	19 ± 1	-8.3 ± 0.8
	CTAN+CH$_3$CN	15 ± 2	19 ± 1	-13 ± 1
	CTAN+CH$_2$Cl$_2$	12.7 ± 0.4	21.1 ± 0.9	-28 ± 1
3[+·]	CAN+ CH$_3$OH	8.4 ± 0.6	19 ± 1	-34 ± 2
	CAN+CH$_3$CN	18.4 ± 0.5	18.8 ± 0.3	-1.3 ± 0.1
	CTAN+CH$_3$CN	17.6 ± 0.4	19.0 ± 0.3	-4.8 ± 0.4
	CTAN+CH$_2$Cl$_2$	14.0 ± 0.3	19.6 ± 0.6	-19 ± 1
4[+·]	CAN+ CH$_3$OH	13.8 ± 0.5	18.3 ± 0.9	-15 ± 1
	CAN+CH$_3$CN	20.0 ± 0.4	19.8 ± 0.2	0.70± 0.05
	CTAN+CH$_3$CN	18.5 ± 0.6	19.2 ± 0.4	-2.3 ± 0.2
	CTAN+CH$_2$Cl$_2$	21.7 ± 0.4	20.7 ± 0.4	3.4 ± 0.3

[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 ±σ. [c] All rate studies were carried out over a temperature range between 15 and 40 °C, [substrate] = 20 mM, [Ce(IV)] = 1 mM. [d] Eyring activation parameters were obtained from $\ln(k_{obs}h/kT) = -\Delta H^{\ddagger}/RT + \Delta S^{\ddagger}/R$. [e] Calculated from $\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$.
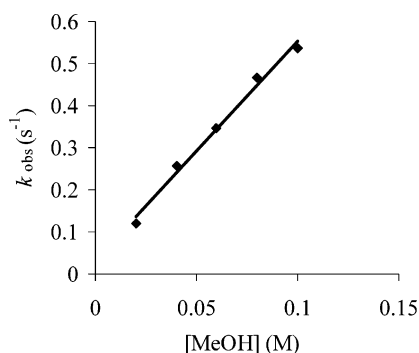
FIGURE 2. Plot of k_{obs} vs [CH$_3$OH] for the decay of **3**[+·] in CH$_2$Cl$_2$.

between radical cations derived from β-diketones and one molecule of CH$_3$OH leads to a more ordered transition state and accelerates the conversion to a radical intermediate through a nucleophile-assisted cleavage of an O−H bond as shown in Scheme 1. Conversely, the non-integer reaction order less than unity for [CH$_3$OH] in the decay of **4**[+·] indicates that CH$_3$OH is less likely to be intimately involved in the decay of radical cations derived from β-keto silyl enol ethers through a direct nucleophilic displacement mechanism.

Studies of radical cations obtained from β-diketones and their structurally related silyl enol ethers in CH$_3$CN and CH$_2$Cl$_2$ show that there is a less pronounced difference between these solvents. Rates of decay are on the order of 2- to 12-fold faster in CH$_3$CN, but there is no clear trend among the two types of radical cations. These findings are consistent with a unimolecular

pathway for cleavage of O−H and O−Si bonds in these solvents. Overall, the combination of present and previous studies shows that the mechanism of decay of radical cations is highly dependent on structure.

One potential problem with the present analysis is the presence of nitrate in the reaction medium. During the oxidation of substrate, Ce(IV) is reduced to Ce(III) and as a result expels 1 equiv of nitrate during the course of the reaction. Although nitrate is not a good nucleophile (or base), the presence of this adventitious anion has the potential to accelerate radical cation decay in nonnucleophilic solvents either through nucleophilic displacement of a silyl or removal of a proton from the respective radical cations. While no products expected from nitrate-induced displacement were isolated, this mechanistic possibility cannot be discounted.

Conclusion

The spectroscopic, kinetic, and mechanistic data described herein collectively show that solvent plays an important role in the rate of the Ce(IV)-mediated oxidation of β-diketones and related β-keto silyl enol ethers. Substrate oxidation and the follow-up decay of radical cations are significantly accelerated in CH$_3$OH compared to CH$_3$CN and CH$_2$Cl$_2$. Kinetic investigations of radical cations derived from β-diketones reveal that a more ordered transition state for the radical cation decay is achieved through heterolytic cleavage of the O−H bond of the intermediate by CH$_3$OH. In the case of radical cations derived from β-keto silyl enol ethers, the rate of desilylation is proportional to the polarity of the solvent medium consistent

SCHEME 1. Transition State for Deprotonation of Radical Cation by CH₃OH Leading to Free Radical Intermediate
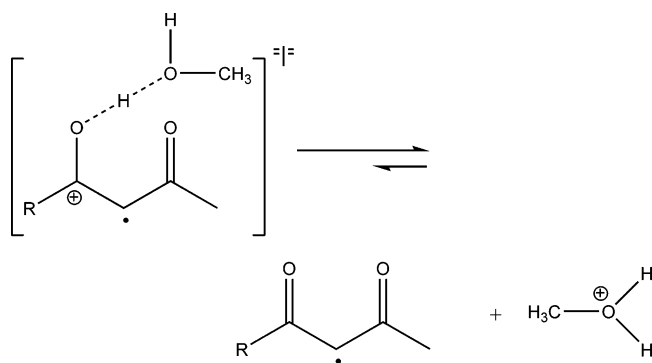
with a mechanism involving unimolecular decay of the intermediate. Remarkably, radical cations derived from β-diketones and β-keto silyl enol ethers are surprisingly stable in methylene chloride. This finding suggests that in nonpolar solvents, radical cations may be the species responsible for C–C bond formation in reactions with olefins. Studies are currently underway to determine whether the solvent milieu alters the intermediate (radical vs radical cation) responsible for bond formation with radicophiles and the degree this plays a role in the solvent-dependent chemoselectivity of many reactions initiated by Ce(IV).

Experimental Section

Materials and General Procedures. Acetonitrile, methanol, methylene chloride, and diethyl ether were distilled before use. All of the other chemical reagents were purchased from Aldrich and used without further purification. Column chromatography was performed with 65–250 mesh silica gel. Compound **1** was prepared by using a previously reported method.[29] CTAN was prepared following the procedure reported by Muathen.[30] ¹H and ¹³C NMR spectra were recorded on a 500 MHz spectrometer. UV–vis experiments were performed on a spectrophotometer that operates in a wavelength range of 190–1100 nm. Oxidation of β-diketones with CAN and CTAN in CH₃CN or CH₂Cl₂ were carried out with use of a recently reported procedure.[16]

Oxidation of 1 with CAN in CH₃OH. Ceric ammonium nitrate (CAN, 4.4 mmol, in 10 mL of MeOH) solution was added to a solution of **1** (2 mmol) in 40 mL of MeOH within 2 min under nitrogen atmosphere. After the mixture was stirred for 4 h at rt, 30

mL of distilled cold water was added to work up the reaction. The organic layer was extracted with 4 × 25 mL of ether, washed with distilled cold water, and dried over MgSO₄. After filtration, the organic solution was concentrated and then subjected to silica gel chromatography to afford 1-acetyl-2-tetralone in 73% isolated yield.[17]

General Procedure for Preparation of 3,3-Dideuterio-2,4-pentanedione. 2,4-Pentanedione (20 mL) was added into D₂O (20 mL), potassium carbonate (2 g), and tetra-*n*-butyl ammonium bromide (1 g) in a round-bottom flask. The mixture was stirred for 3 days at rt. After filtration, the organic layer was extracted with dry diethyl ether and concentrated via rotary evaporation. The synthesis of 3,3-dideuterio-2,4-pentanedione was confirmed by NMR and GC-MS analysis.

Stopped-Flow Studies. Kinetic experiments in methanol, acetonitrile, and dichloromethane were performed with a computer-controlled stopped-flow reaction spectrophotometer. The Ce(IV) oxidant and substrates were taken separately in airtight syringes from a drybox and injected into the stopped-flow system. The cell block and the drive syringes of the stopped-flow reaction analyzer were flushed at least three times with dry and degassed solvents to make the system oxygen free. The concentration of Ce(IV) used for the study was 1 mM. The concentration of substrates was kept high relative to that of [Ce(IV)] (0.02 M) to maintain pseudo-first-order conditions. The rates of Ce(IV) decay were determined from the decrease of the Ce(IV) absorbance at 330 nm. The rates of radical cation formation and radical cation decay were determined from the absorbance change of the radical cation at 460 nm. Reaction rates for the initial oxidation step were determined from the decay of the Ce⁴⁺ absorbance at 330 nm. The decay of Ce(IV) displayed first-order behavior over >4 half-lives for all Ce(IV)–substrate combinations. Time-resolved spectra were obtained from the stopped-flow reaction analyzer at 25 °C. The temperature studies were carried out over a range between 15 and 40 °C with an interval of 5 °C, using a refrigerated circulator connected to the sample-handling unit of the stopped-flow reaction analyzer. The kinetic trace was recorded at a known temperature that was measured by a thermocouple in the reaction cell.

Supporting Information Available: General methods, experimental protocols, and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0625406

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