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Effective thermal oxidation of isopropanol by an NAD^+ model

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Abstract—The reaction of 10-methylacridinium cation (MA^+) with isopropanol in the parent alcohol medium under dark, oxygen-free, and refluxing conditions gave hydride transfer product 10-methyl-9,10-dihydroacridine (MAH). The kinetics of the alcoholic oxidation reaction, including the kinetic isotope effect and the kinetic temperature effect, were determined. Hydride transfer is involved in the rate-determining step.
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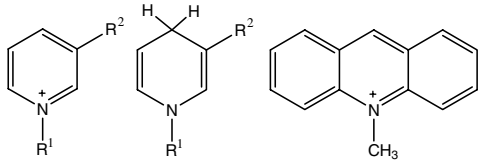
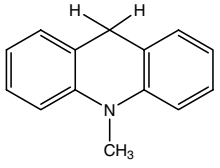
The oxidation of alcohols to the corresponding carbonyl compounds by NAD^+ coenzyme (**1a**, R^1 = adenine dinucleotide, $R^2 = CONH_2$) is an important class of biological reactions.[1,2] This reversible chemical conversion can be mediated by alcohol dehydrogenases. Although biomimetic investigations on the reverse reaction have been well documented employing 1,4-dihydropyridines (**2**, 1,4-DHP) as the reduced form of NAD^+ models and oxidant substrates of various structures including carbonyl compounds,[3–7] very few alcoholic oxidation reactions by N-substituted pyridinium cations are available to elucidate the mechanism of the NAD^+ mediated oxidation. This is largely due to the low redox potentials of the pyridinium cations. Nevertheless, attempts have been made to search the alcohol dehydrogenase model reactions using pyridinium cations as NAD^+ models.[8–11] For example, base catalyzed oxidation of substituted benzyl alcohols by 3-substituted-*N*-heptylpyridinium (**1b–d**, $R^1 = n\text{-}C_7H_{15}$, $R^2 = H$, $CON(CH_2CH_2)_2O$, and $SO_2N(CH_2CH_2)_2O$) gave rise to the corresponding benzaldehyde products.[9] Isolation of the corresponding 1,4-DHP product, however, was not reported.

Another study reported that tracer experiments by treatment of CD_3OLi/CD_3OH with a nicotinamide cation (**1e**, $R^1 = Ph$, $R^2 = CON(CH_3)_2$) led to the isolation of the corresponding 1,4-DHP product, but deuterium was not found to be incorporated into the 4-position of the DHP.[10] Furthermore, reaction in CH_3OLi/CH_3OD system gave the mixture of 2-deuterio- and 6-deuterio-1,4-DHP.[10] This suggests that the 1,4-DHP is not the primary net hydride transfer product. These reactions could not be the models for alcohol dehydrogenase reactions.



1a-f **2 (1,4-DHP)** **3 (MA^+)**



4 (MAH)

In order to avoid the attack by hydride ion to the 2- and 6-positions of its pyridinium ring, the two positions of the model compound need to be blocked. Since another NAD^+ analogue 10-methylacridinium ion (MA^+, **3**) possesses the prerequisite, it was selected in this work for study of the alcohol dehydrogenase model reaction. Note that the model compound is a stronger oxidant than the above-mentioned pyridinium cations (**1**). For example, its hydride affinity is 18 kcal/mol greater than that of 1-benzyl nicotinamide cation (BNA^+, **1f**, $R^1 = CH_2Ph$, $R^2 = CONH_2$).[6]

Keywords: Alcohol oxidation; NAD^+ model; Acridinium cation; Hydride transfer; Kinetics.
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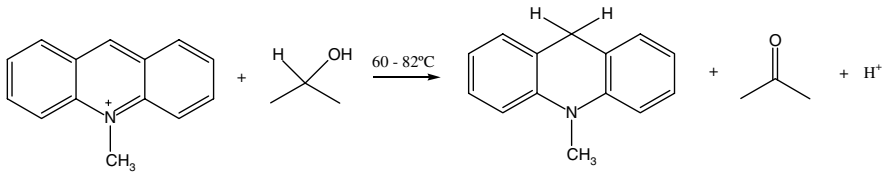
We report the oxidation of isopropanol (*i*-PrOH) via hydride transfer by MA^+ (Eq. 1). The kinetics of the oxidation reaction, including the kinetic isotope effect and the kinetic temperature effect, were determined. The hydride transfer is involved in the rate-determining step. To our knowledge, this is the first observation that alcohol is efficiently oxidized by an NAD^+ model and is the first kinetic measurement of such an alcoholic oxidation reaction.

'intermediate' with quotation mark means that the species involved in the reaction could also be in a side equilibrium with reactants MA^+ and *i*-PrOH.

It has been known that MA^+ can be readily attacked at its 9-position by primary alcohols to form the alcohol adducts (MAOR, **5**).[12] The reversible formation of the isopropanol adduct by treatment of MA^+ with isopropanol at room temperature has also been observed.[12]



(1)

Hundred milliliter *i*-PrOH containing 0.068 mmol $MA^+ClO_4^-$ and 5 ml of H_2O were refluxed under dark and O_2-free conditions for 17 h. The addition of water helped dissolve the MA^+. MAH was isolated from the resulting reaction mixture of MA^+ and MAH by column chromatography. The isolated yield of MAH for this particular reaction time was 48%. The MAH product was characterized by means of NMR spectroscopy. The reaction with isopropanol-d_8/D_2O was also carried out and the deuterium was found to be incorporated into the C-9 position of the product. Replacement of isopropanol-d_8 with normal isopropanol in this experiment did not result in the incorporation of the deuterium (from D_2O) into the C-9 position of the MAH product. These facts indicate that MAH is a primary net hydride transfer product and the hydride transfer reaction may be considered to be a model for the alcohol dehydrogenase reaction.

Base catalyzed hydride transfer reaction was also attempted by adding K_2CO_3 ($[K_2CO_3]/[MA^+] = 2$) to the above reaction system under the same reaction conditions for 20 h. No MAH was obtained.

The UV–vis spectroscopic kinetic scans were recorded for the reaction by determining the spectra of the reaction aliquots at certain time intervals (Fig. 1a). Spectra correspond with the reaction aliquots diluted with isopropanol. The characteristic absorption band with $\lambda_{max} = 358$ nm is attributable to MA^+ and that with $\lambda_{max} = 284$ nm to the MAH product. The kinetic scans are at variance with the spectra of the authentic mixture of MA^+ and MAH (Fig. S1 in Supplementary data) in two points: (1) during the early time period of the reaction, the shape of the spectrum over the MAH absorption wavelength range is sharper and the absorption intensity is unusually high; and (2) the kinetic scans do not have an isosbestic point at 320 nm present in the synthetic ones. These suggest a possible involvement of a reactive 'intermediate' in the reaction system that absorbs over the similar wavelength range as does MAH and therefore masks the MAH absorption band. The

The isopropanol adduct is not as stable as those derived from the primary alcohols due to the steric effect between the secondary isopropoxy group and 1,8-hydrogens of the adduct. We thus infer that the possible 'intermediate' in our reaction would be the corresponding isopropanol adduct, 9-isopropoxy-10-methyl-9,10-

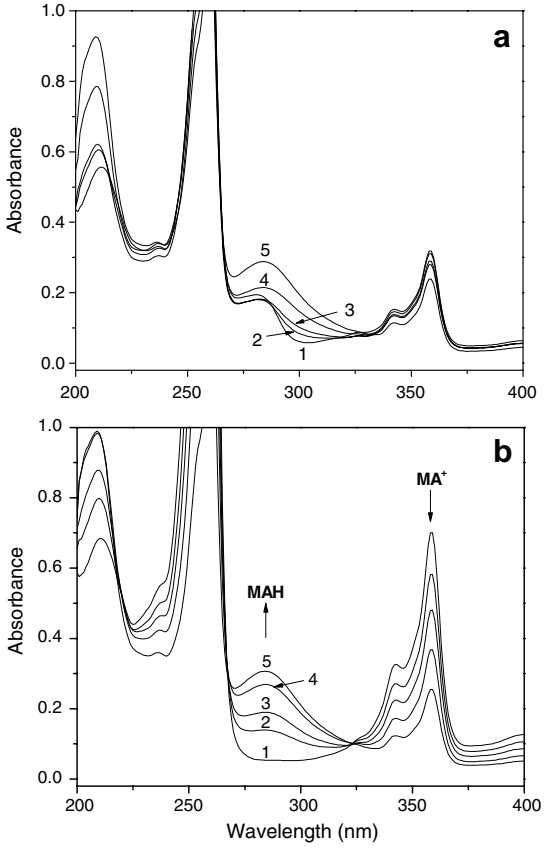
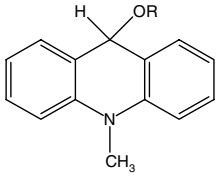


Figure 1. Kinetic scans determined by analysis of the reaction aliquots, taken from the reaction solution at 82 °C with initial $[MA^+] = 0.398$ mM, diluted 10 times with (a) pure isopropanol and (b) isopropanol containing Zn(II) (0.8 mM). Reaction times for spectra 1–5 are 38, 148, 304, 387 and 537 min, respectively.

dihydroacridine (MAOPr-*i*). This class of adducts are known to absorb over a similar wavelength range as does MAH and be sharper in shape than the latter.[13] Also, the adducts decompose to MA^+ and the corresponding alcohols upon encountering acid.[13] In view of this, in an attempt to confirm the presence of MAOPr-*i* in our reaction system and extract the absorption band of MAH that was masked under the spectrum of MAOPr-*i*, we determined the spectra of the reaction aliquots diluted with isopropanol containing a Lewis acid zinc triflate ($Zn(OTf)_2$).[14] As expected, the absorption band at 284 nm weakens and broadens and that at 358 nm strengthens, indicating that the possible adduct intermediate is decomposed to MA^+ and the alcohol (Fig. 1b). This is especially evident for the early time period of the reaction. This, together with other evidence described in the following paragraph, implies that the possible 'intermediate' is MAOPr-*i* and the MAH absorption band can be unmasked by the decomposition of the adduct by acid.



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In order to further confirm the presence of the adduct in the reaction system and the validity of the approach to unmask the MAH absorption band covered under that of the adduct, we determined the spectrum of the MAOPr-*i* synthesized by treatment of MA^+ with *i*-PrOH containing K_2CO_3 (Fig. 2, spectrum 1) and tested the change of the spectrum upon adding Zn(II) ion. The MAOPr-*i* formed was characterized by means of NMR spectroscopy (Fig. S2 in Supplementary data). As expected, the adduct absorption band at 284 nm is similar with that of the reaction aliquot in the early time period of the reaction (for example, spectrum 1 in Fig. 2 vs spectrum 1 in Fig. 1a); and the absorption band weakened and that of MA^+ strengthened upon addition of $Zn(OTf)_2$ (Fig. 2, spectra 2 and 3).

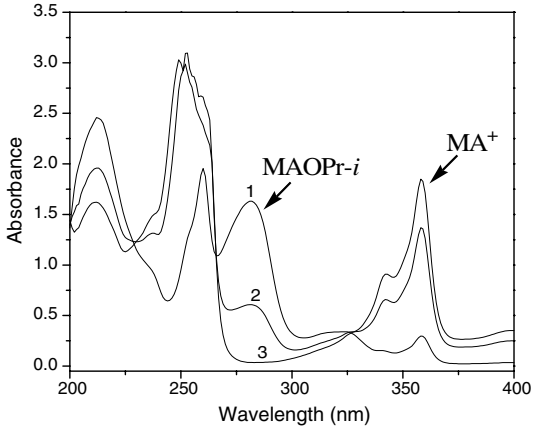

Figure 2. Spectrum of MA^+ (1×10^{-4} M) in isopropanol containing 5×10^{-5} M K_2CO_3 (spectrum 1), and those obtained by adding 5×10^{-5} M Zn(II) (spectrum 2) and 1×10^{-4} M Zn(II) (spectrum 3) to the solution of spectrum 1.

The kinetic scans were thus determined by analysis of the spectra of the reaction aliquot diluted with isopropanol containing Zn(II) (0.8 mM), which excluded the spectrum of the adduct and reflected the genuine kinetic behavior of the interconversion between MA^+ and MAH in the reaction (Fig. 1b). The pseudo first-order rate constants of the hydride reduction of MA^+ by isopropanol at different temperatures were therefore determined in terms of the absorbance decrease with time at 358 nm and are listed in Table 1. Activation parameters calculated from the Arrehenius and Eyring equations and kinetic isotope effect (KIE) are also included in Table 1.

The observed KIE of 3.8 indicates that the hydride transfer step is involved in the rate-determining step. The observed large negative activation entropy ($\Delta S^{\ddagger} = -161.5$ J/mol K) implies that the transition state in the hydride transfer reaction is of a tight structure. At present, whether the observed alcohol adduct of the MA^+ is on the reaction coordinate to form MAH or in a side equilibrium with reactants remains unknown. Attempts to isolate the adduct from the reaction system failed. Note that the hydride transfer reaction cannot take place within the adduct for it requires a four-membered ring transition state. This can be supported by the failure to observe the MAH formation from an attempted reaction between MA^+ and isopropanol in the presence of K_2CO_3 where MAOPr-*i* is stably formed. This implicates that the adduct would have to be converted to another reaction intermediate prior to the hydride transfer step if it were on the way to form MAH (Eq. 2), and the intermediate would have to contain the structure of MA^+ to ensure that in basic isopropanol medium the second equilibrium favors the adduct formation so that the MAH production is depressed. On the other hand, this also suggests that the adduct may not be a significant intermediate in the reaction. In Eq. 2, the hydride transfer step is described as an irreversible step as under our reaction conditions the acetone product would be removed upon formation by evaporation from the reaction system. The detailed hydride transfer reaction mechanism is under investigation.

Table 1. The effect of temperature and isopropanol-d_8 on the pseudo first-order rate constant of the hydride transfer reaction[a]

Temp (°C)	$k_{obs} \times 10^3$ (min^{-1})[b]	KIE
82	1.83 ± 0.17	
74	0.915 ± 0.050	
67	0.579 ± 0.016	3.8
60	0.455 ± 0.033	
	$E_a = 62.6$ kJ/mol	
	$\Delta H^{\ddagger} = 59.7$ kJ/mol	
	$\Delta S^{\ddagger} = -161.5$ J/mol K	

[a] $[MA^+ClO_4^-] = 0.398$ mM in isopropanol containing 4.76% (v/v) water.

[b] Based on three determinations.

$$MA^+ + i\text{-PrOH} \underset{+H^+}{\overset{-H^+}{\rightleftharpoons}} MAOPr\text{-}i \rightleftharpoons \text{intermediate} \rightarrow MAH + \text{acetone} \quad (2)$$

It should be mentioned that the hydride reduction of BNA^+ (**1f**) by alkyl alcohols including *i*-PrOH has also been previously attempted by the action of various Zn(II) complexes, but was inefficient.[15–17] The addition of the Zn(II) complexes was meant to imitate the complexed zinc environment in the active site of the alcohol dehydrogenases. Lewis acid of Zn(II) complexes is believed to catalyze the hydride transfer from alcohol to NAD^+ by the formation of a reactive zinc alkoxide intermediate through Lewis acid catalyzed deprotonation of the alcohol.[1,2] Our observation of the hydride reduction of MA^+ by isopropanol may provide a model reaction for possible study of the role of the Zn(II) complexes in the biological hydride transfer reaction.

To summarize, the hydride transfer reaction from *i*-PrOH to an NAD^+ model (MA^+) has been achieved. The rate constant of the reaction was determined. The isopropanol alcohol adduct of MA^+ is involved in the reaction system. Whether the adduct is on the way to form MAH or in a side equilibrium with reactants remains unclear. This is the first observation that alcohol was effectively oxidized via hydride transfer by an NAD^+ model. Although the isotopic labeling experiment suggests that MAH is the primary net hydride transfer product, whether the alcoholic oxidation reaction is a genuine alcohol dehydrogenase model reaction would only be finally concluded when the reaction mechanism is completely understood. Furthermore, the present work has provided a kinetic approach in investigating alcoholic oxidations by various NAD^+ models catalyzed by diversified potential Zn(II) complex catalysts in various solvents. Further such studies, including the mechanistic investigation of the reaction described in this work, are currently in progress in this lab in an attempt to gain biomimetic understanding of this important biological alcoholic oxidation reaction.

Acknowledgments

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Supplementary data

Synthesis of the reactants, product structure analysis, determination of the rate constants and spectroscopic data of the relevant compounds are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.07.038.

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