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Mechanism of the Oxidation of Alcohols by Oxoammonium Cations

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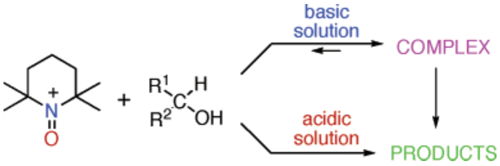

The mechanism of the oxidation of primary and secondary alcohols by the oxoammonium cation derived from 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) has been investigated computationally at the B3LYP/6-31+G* level, along with free energies of solvation, using a reaction field model. In basic solution, the reaction involves formation of a complex between the alkoxide anion and the oxoammonium cation in a pre-oxidation equilibrium wherein methoxide leads to a much larger formation constant than isopropoxide. The differences in free energy of activation for the rate-determining hydrogen transfer within the pre-oxidation complexes were small; the differences in complex formation constants lead to a larger rate of reaction for the primary alcohol, as is observed experimentally. In acidic solution, rate-determining hydrogen atom transfer from the alcohol to the oxoammonium cation had a large unfavorable free energy change and would proceed more slowly than is observed. A more likely path involves a hydride transfer that would be more rapid with a secondary alcohol than primary, as is observed. Transition states for this process were located.

Introduction

The oxidation of alcohols by oxoammonium salts,[1] first reported by Golubev more than 40 years ago,[2] has become a widely used and environmentally benign method for the conversion of primary and secondary alcohols to aldehydes and ketones.[3] The oxidation of an alcohol by using a stoichiometric quantity of a preformed oxoammonium salt is readily accomplished.[4] More commonly, oxidations are conducted via a catalytic process that involves in situ generation of the oxoammonium cation by one-electron oxidation of a small quantity of a nitroxide, such as 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), either electrochemically[5] or with a stoichiometric quantity of a primary oxidant,[3] such as sodium hypochlorite.[6] The rate of oxidation of both primary and secondary alcohols by oxoammonium cations increases with increasing pH of the

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[1] Salts containing the N=O cation derived from stable nitroxides such as 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) by one-electron oxidation are referred to as oxoammonium salts. However, it should be noted that terms such as nitrosonium, immonium oxide, iminoxyl, and oxoamminium have been used in the older literature to describe such species.

[2] Golubev, V. A.; Rozantsev, É. G.; Neiman, M. B. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1965**, 1927; *Bull. Akad. Sci. USSR, Div. Chem. Sci.* **1965**, 1898.

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[4] (a) Miyazawa, T.; Endo, T.; Shiihashi, S.; Okawara, M. *J. Org. Chem.* **1985**, *50*, 1332. (b) Bobbitt, J. M. *J. Org. Chem.* **1998**, *63*, 9367 and references cited therein. (c) Bobbitt, J. M.; Merbouh, N. *Organic Syntheses*; Wiley: New York, 2005; Vol. 82, p 80.

[5] (a) Semmelhack, M. F.; Chou, C. S.; Cortes, D. A. *J. Am. Chem. Soc.* **1983**, *105*, 4492. (b) Kishioka, S.; Ohki, S.; Ohsaka, T.; Tokuda, K. *J. Electroanal. Chem.* **1998**, *452*, 179.

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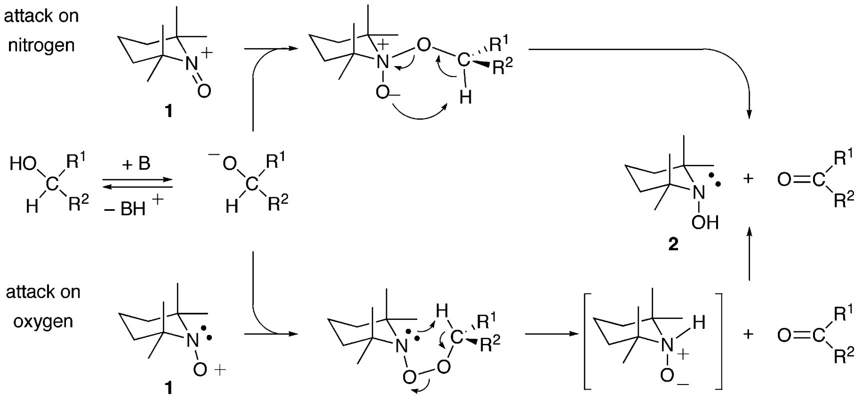
SCHEME 1. Suggested Oxidation Mechanisms in Basic Solution



reaction medium and, for this reason, most catalytic processes are carried out under basic conditions. Irrespective of the technique employed for the oxidation, the oxoammonium cation is the active oxidant.

A particularly intriguing feature of these oxidations is the variation in chemoselectivity with pH: in basic solution, primary alcohols are oxidized more rapidly than are secondary alcohols, whereas in a neutral or acidic medium, the relative rates are reversed.[3] Pioneering mechanistic studies by Golubev's group, using stoichiometric 2,2,6,6-tetramethylpiperidine-1-oxoammonium chloride and perchlorate salts, revealed that at least two mechanisms are operative: (1) a slow oxidation, essentially pH independent at low pH (viz. pH $<\sim 4$) favors oxidation of secondary alcohols and (2) a much more rapid reaction at higher pH (viz. pH $>\sim 5$) favors oxidation of primary alcohols.[7] A 1986 investigation by Semmelhack and co-workers of alcohol oxidation under basic conditions using electrochemically generated 2,2,6,6-tetramethylpiperidine-1-oxoammonium cation (**1**) led to the reasonable suggestion that the reaction in basic solution is initiated, as illustrated in Scheme 1, by formation of a reactive complex generated by nucleophilic attack of an alcoholate anion on either the nitrogen atom or the oxygen atom of **1**.[8] Rate-determining intramolecular proton transfer within either intermediate complex would serve to deliver the carbonyl compound and a molecule of hydroxylamine (**2**). Semmelhack favored the route that involves alkoxide attack on the nitrogen atom of **1** but noted that the alternative pathway could not be excluded based on the available data.[8] With minor modification, to accommodate the possibility of intermolecular removal of the C−H hydrogen by base[9] and to note that steric effects should influence ease of formation of the putative pre-oxidation complex between an alkoxide and **1**,[10] the Semmelhack proposal (Scheme 1) has been accepted as the likely mechanism for alcohol oxidation by an oxoammonium cation in the presence of base.[3] The mechanism of the oxidation in acidic or neutral solution, as well the origin of the variation in chemoselectivity with pH, has not been addressed.

Given current interest in the oxidation of alcohols by oxoammonium cations, it seemed worthwhile to investigate the ability of molecular orbital theory to provide insight into the mechanism(s) of alcohol oxidation by the prototypical 2,2,6,6-tetramethylpiperidine-1-oxoammonium cation (**1**).

Results and Discussion

To further examine the oxidation of alcohols by oxoammonium salts, we have carried out calculations at the B3LYP/6-31+G* level.[11] Although this is a fairly small basis set, it should be adequate to distinguish among various mechanistic proposals. As detailed below, the results of this study support the intermediacy of a pre-oxidation complex formed by alkoxide attack on the nitrogen atom of **1** and indicate that it is the relative stability of these complexes that is largely responsible for the rapid oxidation of primary alcohols in basic solution. A mechanism for the pH independent pathway in neutral or acidic solution has also been identified.

Oxidations in Basic Solution. The mechanism of the oxidation in basic solution was first addressed: methoxide, ethoxide, and isopropoxide were chosen as representative substrates and the gas-phase energies and enthalpies of these alkoxides, as well as that of 2,2,6,6-tetramethylpiperidine-1-oxoammonium cation (**1**) and the oxidation products, were determined at the B3LYP/6-31+G* level. Since the free energies are the more important quantities in studying reactions, vibrational frequencies were determined for all compounds at the same level. The calculated frequencies were used to give an estimate of the zero point energy (ZPE), and the free energy changes on going from 0 (corresponding to the computational results) to 298 K (room temperature) were also obtained with these frequencies. Computational details and a summary of these calculations, including calculated absolute energies, zero point energies, and detailed structural data for all species, may be found in the Supporting Information.

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(7) Golubev, V. A.; Borislavskii, V. N.; Aleksandrov, A. L. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1977**, 2025; *Bull. Akad. Sci. USSR. Div. Chem. Sci.* **1977**, 1874.

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(11) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision C.0; Gaussian, Inc.: Wallingford, CT, 2004.

TABLE 1. Energy Changes (kcal/mol) for Reactions in Basic Media[a]

reaction	ΔH_{gas}	ΔG_{gas}	ΔG_{soln}[b]
1 + $\mathrm{MeO^-}$ → complex	−141.1	−128.4	−17.9
1 + $\mathrm{EtO^-}$ → complex	−135.4	−122.3	−13.8
1 + *i*-$\mathrm{PrO^-}$ → complex	−128.3	−114.6	−9.6
$\mathrm{MeO^-}$ complex → TS	4.3	4.7	4.5
$\mathrm{EtO^-}$ complex → TS	3.1	3.9	3.4
i-$\mathrm{PrO^-}$ complex → TS	2.1	2.3	1.7
$\mathrm{MeO^-}$ TS → products	−22.4	−30.5	−35.7
$\mathrm{EtO^-}$ TS → products	−30.1	−44.2	−50.0
i-$\mathrm{PrO^-}$ TS → products	−38.1	−52.9	−58.4
$\mathrm{MeO^-}$ on N of **1** vs $\mathrm{MeO^-}$ on O of **1**	10.5	8.3	9.1

[a] ΔH and ΔG values are corrected for both differences in ZPE and the change in enthalpy on going from 0 (corresponding to the calculations) to 298 K (the temperature at which oxidations are conducted). [b] Acetonitrile solution.

TABLE 2. Energy Changes (kcal/mol) for Reactions in Acidic Media[a]

reaction	ΔH_{gas}	ΔG_{gas}	ΔG_{soln}[b]
1 + MeOH → radicals	35.8	35.0	32.0
1 + *i*-PrOH → radicals	31.6	30.4	28.8
MeOH → $\mathrm{CH_2OH}$ + H	93.0	92.9	91.9
i-PrOH → $\mathrm{Me_2COH}$ + H	88.9	88.2	88.7
1 + H → radical cation of **2**	57.2	57.8	59.9
1 + MeOH → TS	27.1	39.7	42.8
1 + *i*-PrOH → TS	12.7	25.1	28.1

[a] ΔH and ΔG values are corrected for both differences in ZPE and the change in enthalpy on going from 0 (corresponding to the calculations) to 298 K. [b] Acetonitrile solution.

As illustrated in Scheme 1, the formation of pre-oxidation complex between an alkoxide and **1** could occur by attack on the nitrogen atom or the oxygen atom of the cation. For each of these modes of attack, two stereochemically distinct pathways were considered: the alkoxide may approach the electrophilic centers of **1** from the side of the equatorial methyl groups or from the direction of the axial methyl groups. The reaction of methoxide with **1** was chosen for initial study and the results of these calculations, summarized in Table S1 of the Supporting Information, demonstrate that the complex formed by attack on nitrogen from the equatorial direction (as depicted in Scheme 1) is the most stable of the four potential pre-oxidation intermediates. This result is perhaps not surprising given that the nitrogen atom of **1** bears most of the positive charge and attack on the oxygen atom produces a peroxide with a relatively weak oxygen−oxygen bond. In fact, the more stable complex generated by methoxide attack on oxygen has a higher energy than the transition state for conversion of the nitrogen centered complex to formaldehyde and hydroxylamine (vide infra). Clearly, the peroxide complex cannot be involved in the oxidation of methoxide and it seems reasonable to assume, as suggested by Semmelhack,[8] that attack on the electrophilic nitrogen position of **1** is the preferred route to a pre-oxidation complex for all alkoxides. The reactions of ethoxide and isopropoxide with **1** to give analogous pre-oxidation intermediates were investigated, and the results are summarized in Table 1. Structures of the lowest energy complexes generated in the reactions of **1** with methoxide, ethoxide, and isopropoxide are illustrated in Figure 1.

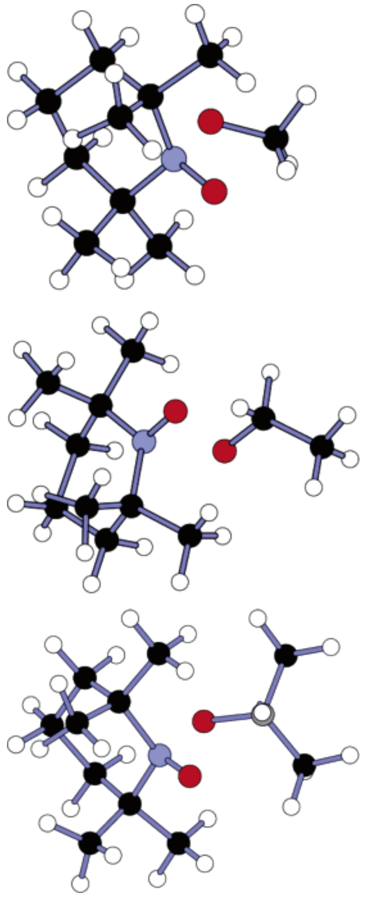

FIGURE 1. Structures of the lowest energy complexes generated in the reactions of **1** with $\mathrm{MeO^-}$ (top), $\mathrm{EtO^-}$ (middle), and *i*-$\mathrm{PrO^-}$ (bottom); the nitrogen atom is blue, oxygen is red.

A difficulty with analysis of energies derived from calculations involving reactions of ions to give a neutral product is the relatively high energies of the ions in the gas phase. The oxidations being examined are conducted in solution and solvation serves to stabilize ions to a significant extent. Prior mechanistic studies of the oxidation of alcohols by oxoammonium cations have been conducted with acetonitrile as solvent[7,8] and for this reason it seemed appropriate to evaluate the effect of $\mathrm{CH_3CN}$ on the calculated energies. To this end, the calculations were extended to give the free energies of solvation of the relevant species in $\mathrm{CH_3CN}$ by using the IEPCM reaction-field model in Gaussian.[11] The calculated free energies of solvation, given in Table S1 of the Supporting Information, were used to compute the ΔG values in acetonitrile solution for the reactions summarized in Table 1.

The most striking feature of the computed free energy changes attending formation of the pre-oxidation intermediates from the reaction of **1** with alkoxides is their large and negative values.[12] The sizable ΔG for adduct formation make it possible to form significant amounts of such complexes even in relatively weakly basic solutions where the concentrations of the alkoxide will be low: this is perhaps best appreciated by reference to the computed equilibrium constants for complex formation at room temperature summarized in Scheme 2. It is significant that the

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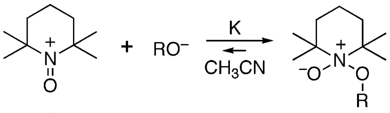
[12] In this connection, it might be noted that 2,2,6,6-tetramethylpiperidine-1,1-dioxide salts precipitate upon addition of 2,2,6,6-tetramethylpiperidine-1-oxoammonium salts to concentrated, aqueous solutions of NaOH or KOH. See: (a) Sen, V. D.; Golubev, V. A.; Kosheleva, T. M. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1978**, 2001; *Bull. Akad. Sci. USSR, Div. Chem. Sci.* **1978**, 1847. (b) Golubev, V. A.; Sen, V. D.; Rozantsev, E. G. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1978**, 2091; *Bull. Akad. Sci. USSR, Div. Chem. Sci.* **1978**, 1927.

SCHEME 2. Complex Formation Constants



1

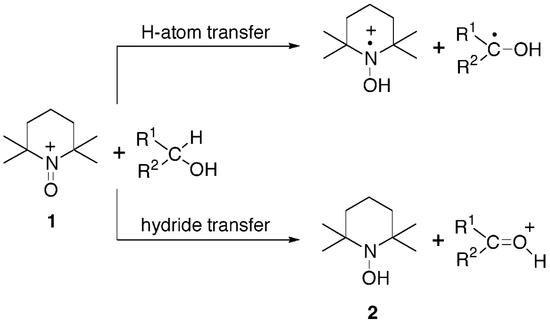
RO^-	K
MeO^-	1.3×10^{13}
EtO^-	1.3×10^{10}
i-PrO^-	1.1×10^{7}

favorable ΔG for complex formation decreases appreciably, and in a rather regular fashion, as the steric bulk of the alkoxide increases: MeO^- ($\Delta G = -17.9$ kcal/mol) > EtO^- ($\Delta G = -13.8$ kcal/mol) > *i*-PrO^- ($\Delta G = -9.6$ kcal/mol). As a result, the equilibrium constant for generation of the MeO^- complex is approximately 10^6 times larger than that for formation of the *i*-PrO^- complex (Scheme 2). These large differences in complex stability, which are presumably related to unfavorable steric interactions in the more crowded isopropoxide complex as suggested some time ago by van Bekkum and co-workers,[10] offer a compelling rationale for the observation that primary alcohols are oxidized more rapidly than are secondary alcohols in basic solution.

The conversion of the pre-oxidation complex to a molecule of **2** and an aldehyde or ketone is a highly exothermic process for each of the alcohols studied (Table 1). Transition states for the rate-determining conversion of the pre-oxidation complexes to hydroxylamine (**2**) and carbonyl products were located at the same level by using the method of Schlegel et al.[13] and were shown to have one imaginary frequency corresponding to transfer of a hydrogen from C(1) of the alcohol to the oxygen of **1**. The gas-phase energies of the transition states and their imaginary frequencies are given in Table S1 of the Supporting Information; the structures of the transition states are shown in Figure 2. The change in shape and dipole moment on going from the complexes to their transition states are quite small, and the relative energies should not be significantly affected by the solvent. Nonetheless, the free energies of solvation of the transition states in CH_3CN were evaluated by using the IEPCM reaction-field model, giving the results summarized in Table 1.

The calculated activation energies (Table 1, $\Delta G^{\ddagger} = \Delta G$ for complex → TS) are fairly low, and this is in accord with the rapid oxidation of alcohols in basic solution. As might be anticipated, rate-determining transfer of a hydrogen within the isopropoxide complex has a lower activation free energy ($\Delta G^{\ddagger} = 1.7$ kcal/mol) than does the transfer within either the ethoxide complex ($\Delta G^{\ddagger} = 3.4$ kcal/mol) or the methoxide complex ($\Delta G^{\ddagger} = 4.5$ kcal/mol). In short, it is easier to oxidize the secondary alcohol by hydrogen atom transfer from within the adduct. However, the rate of alcohol oxidation in basic solution is a function of both the activation free energy, or equivalently the rate constant (k), and the concentration of the complex (i.e., $-d[ROH]/dt = k[\text{complex}]$).[14] It would seem that, to the extent primary alcohols are oxidized more rapidly than secondary alcohols in basic solution, the chemoselectivity of the process is largely a consequence of the considerable differences in stability of complexes generated from alkoxides derived from primary or secondary alcohols. Moreover, at a given pH there will be a higher concentration of a primary alkoxide than of secondary alkoxide because primary alcohols are somewhat more acidic in solution than are secondary alcohols.[15]

SCHEME 3. Suggested Oxidation Mechanisms in Acidic Solution



Oxidations in Acidic Solution. As noted in the introduction, oxidations of alcohols by oxoammonium salts in acidic solution are significantly slower processes than are oxidations at higher pH.[3] Moreover, at pH <~4, the oxidation of isopropyl alcohol by **1** is more rapid than is the oxidation of methanol.[7] Evidently, alcohol oxidation in a suitably acidic medium does not involve formation of a pre-oxidation complex between alkoxide and the oxoammonium cation of the sort discussed above. Two conceivable mechanisms for the oxidation of alcohols by **1** that do not involve generation of a pre-oxidation adduct are illustrated in Scheme 3.

The hydrogen atom transfer mechanism depicted in Scheme 3 generates a carbon-centered alcohol radical and the radical cation of **2**. This mechanistic possibility was investigated by computing the enthalpy and free energy changes for reactions of **1** with MeOH and *i*-PrOH. The energies of the relevant species were evaluated at the B3LYP/6-31+G* level, the free

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[13] (a) Peng, C.; Ayale, P. Y.; Schlegel, H. B.; Frisch, M. J. *J. Comput. Chem.* **1996**, *17*, 49. (b) Peng, C.; Schlegel, H. B. *Isr. J. Chem.* **1994**, *33*, 449.

[14] It is of some interest to compare the computational results to the experimentally observed rates of oxidation in basic solution. The second-order rate constant for the oxidation of *i*-PrOH by **1** in aqueous acetonitrile solution has been reported by Golubev to increase with increasing pH: at pH 8.0, the rate of the oxidation is $\sim 3 \times 10^{-2}$ L mol^{-1} s^{-1}.[7] Since $-d[i\text{-PrOH}]/dt = k[\text{complex}] = kK[i\text{-PrO}^-][\mathbf{1}]$, one may approximate the rate of the oxidation at a given pH using the first-order rate constant (k) obtained from the computed activation free energy for conversion of the isopropoxide complex to products at room temperature (viz., 3.7×10^{11} s^{-1}) and a value for the equilibrium constant (K) for complex formation (viz., $K = 1.1 \times 10^7$ for the isopropoxide complex). Thus, $[\text{complex}] = K[i\text{-PrO}^-][\mathbf{1}]$ and, since $[i\text{-PrO}^-] = K_a[i\text{-PrOH}][OH^-]$, where the p$K_a$ for *i*-PrOH is ~16.5,[15] $-d[i\text{-PrOH}]/dt = kK[i\text{-PrO}^-][\mathbf{1}] = kKK_a[i\text{-PrOH}][\mathbf{1}][OH^-] = (3.7 \times 10^{11}\ s^{-1})(1.1 \times 10^7)(3.2 \times 10^{-17})[i\text{-PrOH}][\mathbf{1}][OH^-] \approx 130[i\text{-PrOH}][\mathbf{1}][OH^-]$. At pH 8.0, $[OH^-] = 10^{-6}$, the computed rate is 1.3×10^{-4} L mol^{-1} s^{-1}. Given the approximations made in calculation of the pre-oxidation complex stability and the activation energy for conversion to product, the agreement between the computed and experimental rate for the oxidation of *i*-PrOH by **1** is encouraging. The observed rate of oxidation of MeOH at pH 8 is about 250 times that for *i*-PrOH.[7] Using p$K_a \approx 15.2$ for MeOH,[15] and the calculated complex formation constant (viz., $K = 1.3 \times 10^{13}$) and rate constant for the oxidation (viz., 3.1×10^9 s^{-1}), the rate of oxidation of MeOH is calculated to be $\sim 2 \times 10^5$ greater than that for *i*-PrOH. The large formation constant for the methoxide complex (10^6 times larger than that for the isopropoxide complex) requires that the rate of formation of this complex is much faster with MeO^- than with *i*-PrO^-. It is likely that the formation of the methoxide complex is close to diffusion controlled and thus partially rate determining. If this is the case, the rate of MeOH oxidation will be slower than that calculated.

[15] Smith, M. B. *March's Advanced Organic Chemistry*; Wiley: Hoboken, NJ, 2007; p 362.

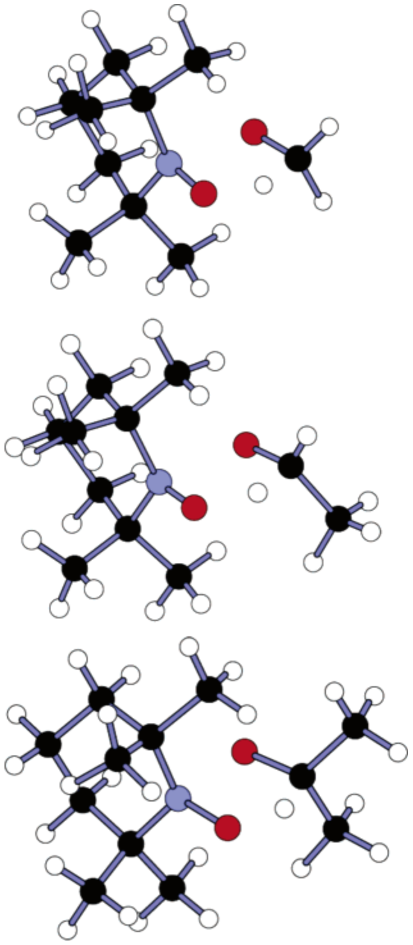

FIGURE 2. Structures of the transition states for hydrogen transfer within the methoxide complex (top), the ethoxide complex (middle), and the isopropoxide complex (bottom).

energies of solvation in CH_3CN were computed with use of the IEPCM reaction-field model, and ΔG values for transfer of a hydrogen atom from each alcohol to **1** in CH_3CN solution were obtained. The results of these calculations, summarized in Table 2, demonstrate that the hydrogen atom transfer reactions are highly endothermic. The relatively high C−H bond dissociation energies of the alcohols (viz. ∼90 kcal/mol) and the much lower bond dissociation energy of the radical cation product account for the large, positive ΔG values. Thus, it appears that the reaction of alcohols with **1** in acidic solution must involve a two-electron oxidation.

Transition states for the reactions of MeOH and *i*-PrOH with **1** in acetonitrile solution, corresponding to the hydride transfer mechanism illustrated in Scheme 3, were located; each had a single imaginary frequency (Table S1, Supporting Information) corresponding to transfer of the C−H hydrogen to the oxygen of **1**. The structures of the transition states for oxidation of MeOH and *i*-PrOH are shown in Figure 3, and the activation energies required for the oxidations are summarized in Table 2. An obvious difficulty with the computed activation energies is the formation of a high-energy protonated aldehyde or ketone in the oxidation step. In solution, the neutral carbonyl compound is the actual product and the developing protonated carbonyl will surely be stabilized by proton transfer to solvent but this is difficult to model computationally. Nonetheless, the relative activation energies (Table 2) are instructive: oxidation of *i*-PrOH in acetonitrile solution to give protonated acetone has calculated $\Delta G^{\ddagger}$ (∼28 kcal/mol) that is considerably lower than that for the oxidation of MeOH to protonated formaldehyde ($\Delta G^{\ddagger} \approx 43$ kcal/mol) as would be expected for an oxidation that involves formal transfer of a hydride. This result is in qualitative agreement with the experimental observation that secondary alcohols are oxidized more rapidly than are primary alcohols in acidic solution.[3]

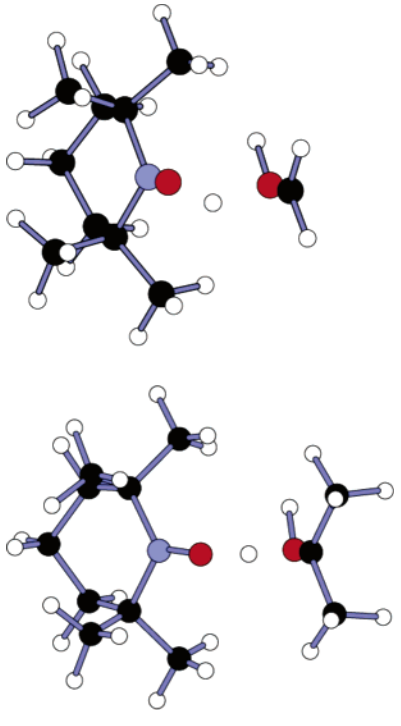

FIGURE 3. Structures of the transition states for oxidation of MeOH (top) and *i*-PrOH (bottom) in acidic solution.

Conclusions

The computational results discussed above indicate that, as originally suggested by Semmelhack and co-workers,[8] the oxidation of an alcohol by an oxoammonium salt in basic solution involves formation of a rather stable pre-oxidation intermediate generated via alkoxide attack on the electrophilic nitrogen atom of the oxoammonium cation as illustrated in Scheme 2. The sizable equilibrium constants for formation of such pre-oxidation complexes (Figure 1) decrease as the steric bulk of the alkoxide increases and these large differences in complex stability (Scheme 2) offer a rationale for the observation that primary alcohols are oxidized more rapidly than are secondary alcohols in basic solution. Indeed, the activation free energies ($\Delta G^{\ddagger}$) for rate-determining transfer of a hydrogen from within the pre-oxidation intermediates (Figure 2), which delivers the corresponding aldehyde or ketone and hydroxylamine, are fairly low (Table 1) as would be expected for the rather rapid oxidation of alcohols in basic solution. Thus, although rate-determining transfer of a hydrogen within the isopropoxide complex has a lower computed $\Delta G^{\ddagger}$ than does analogous transfer from within either the ethoxide or methoxide complex, the very considerable differences in complex stability suggest that the rate of oxidation of MeOH or EtOH in basic solution should be faster than that of *i*-PrOH as observed experimentally.

The much slower oxidation of alcohols in acidic solution, wherein the concentration of alkoxide is negligible, likely involves bimolecular transfer of a hydride from the α-carbon of alcohol to the oxygen of the oxoammonium cation as illustrated in Figure 3.

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Supporting Information Available: A summary of the calculations, including computed energies, imaginary frequencies for transition states, free energies of solvation in acetonitrile solution, and computed atomic coordinates for all species. This material is available free of charge via the Internet at http://pubs.acs.org.

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