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# Activation of the C−H Bond by Electrophilic Attack: Theoretical Study of the Reaction Mechanism of the Aerobic Oxidation of Alcohols to Aldehydes by the Cu(bipy)$^{2+}$/2,2,6,6-Tetramethylpiperidinyl-1-oxy Cocatalyst System

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We have investigated the reaction mechanism of the selective aerobic oxidation of primary alcohols into aldehydes using a bipy-copper complex and the 2,2,6,6-tetramethylpiperidinyl-1-oxy (TEMPO) radical as cocatalysts (Gamez et al. *Chem. Commun.* **2003**, 2412−2415) and compared it to the well-known oxidation by the TEMPO$^+$ ion. Our theoretical investigation shows that (a) the oxidation of alcohols to aldehydes by uncoordinated TEMPO$^+$ takes place by electrophilic attack on the C−H$_\alpha$ bond of the alcohol; (b) the Cu(bipy)$^{2+}$ complex has two functions, namely, (1) it acts as a template that brings TEMPO and the (deprotonated) alcohol in proximity by coordinating these moieties in adjacent coordination sites, and (2) it oxidizes the TEMPO radical to (coordinated) TEMPO$^+$ ion. The H abstraction from alcohol by TEMPO$^+$ then proceeds as an intramolecular reaction, very much analogous to one of the reaction pathways with free TEMPO$^+$ and with a remarkably low barrier. We stress that compared to other A−H bonds (A=C, N, O, F), the relatively high-lying C−H bonds are particularly susceptible to electrophilic attack, and notably the C−H$_\alpha$ bond next to the O in an alcohol is so because it is pushed up by an O lone pair. Electrophilic attack, being common to the particular catalytic system studied in this paper and the well-known biotic and abiotic oxidation catalysis by heme and non-heme complexes of the ferryl (Fe$^{IV}$O$^{2+}$) ion, appears to be a unifying electronic structure principle of C−H$_\alpha$ hydroxylation and oxidation reactions.

## Introduction

Selective oxidation of alcohols to carbonyl compounds is one of the most important functional transformations in organic chemistry.[1] In nature, copper enzymes are known to activate dioxygen for highly selective transformations under mild reaction conditions and in aqueous solutions.[2] It is therefore surprising that only a limited number of cheap and "green" copper catalyzed oxidative transformations of alcohols by molecular dioxygen[3−6] or by hydrogen peroxide[7−14] have been reported so far.

A very mild method for the selective aerobic oxidation of primary alcohols to aldehydes with excellent conversions has been recently developed by Gamez et al.[15] following earlier work of Sheldon and cowokers.[16] The catalytic procedure is based on the CuBr$_2$ (5 mol %) - bipy (bipy = 2,2′-bipyridine) (5 mol %) system with TEMPO (TEMPO = 2,2,6,6-tetramethylpiperidinyl-1-oxy) and a base, $^t$BuOK, as cocatalysts

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**Scheme 1.** $CuBr_2$-Catalyzed Oxidation of Primary Alcohols As Proposed by Gamez et al.[21]

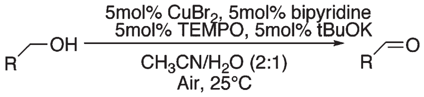


**Table 1.** $CuBr_2$-Catalyzed Oxidation of Benzyl Alcohol to Benzaldehyde[a]

| entry | bipy | TEMPO | $^t$BuOK | time (h) | conversion (%) |
|---|---|---|---|---|---|
| 1 | no | yes | yes | 1.5 | 6 |
| 2 | yes | no | yes | 1.5 | |
| 3 | yes | yes | no | 1.5 | 27 |
| 4 | yes | yes | no | 24 | 100 |
| 5 | yes | yes | yes | 1.5 | 83 |
| 6 | yes | yes | yes | 2.5 | 100 |

[a] Based on GC, the selectivity is $>99\%$.[21]

(5 mol % each) in an acetonitrile/water (2:1) solvent mixture in air at 25 °C (see Scheme 1). Various benzylic, allylic, *and* aliphatic primary alcohols have been successfully oxidized to the corresponding aldehydes with no sign of overoxidation whereas no reaction was observed with secondary alcohols.

The efficiency of the catalytic activity relies on the presence of a N-donor ligand, which is able to stabilize Cu(II), and on the presence of a strong base which is believed to be responsible for alcohol deprotonation (see Table 1). In addition, the experimental studies have shown that copper and TEMPO are both crucial for the oxidation, since no reaction is observed when one of them was missing (see Table 1). But the mechanism of this reaction remains unclear: what is the exact role of TEMPO? And of the copper? Why is this catalytic system so selective?

The first selective copper/TEMPO catalyzed oxidation of allylic, benzylic, *and* aliphatic primary alcohols to aldehydes has been proposed by Semmelhack et al.[3] The room temperature oxidation of primary alcohols by dioxygen is promoted by a catalyst mixture of cupric chloride ($CuCl_2$), nitroxyl radical (TEMPO), and a base ($CaH_2$) in acetonitrile. Semmelhack et al. proposed the following catalytic sequence:

$$4Cu^{2+} + 4TEMPO \rightarrow 4Cu^{+} + 4TEMPO^{+}$$

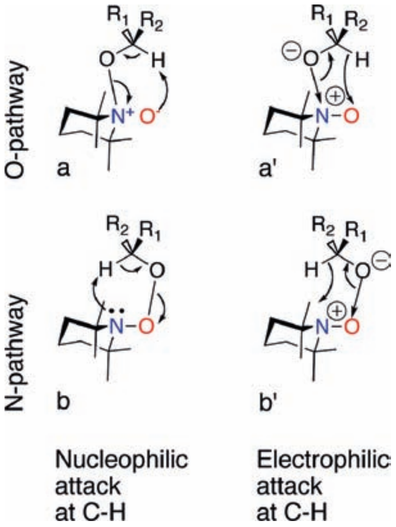
$$2TEMPO^{+} + 2RCH_2OH \rightarrow 2TEMPOH + 2RCHO + 2H^{+}$$

$$2TEMPOH + 2TEMPO^{+} \rightarrow 4TEMPO + 2H^{+}$$

$$4Cu^{+} + O_2 + 4H^{+} \rightarrow 4Cu^{2+} + 2H_2O$$

In this proposal, the cupric ion $Cu^{2+}$ effects a one-electron oxidation of TEMPO to the nitrosonium ion $TEMPO^+$; the alcohol is then oxidized by $TEMPO^+$ generating the aldehyde and the hydroxylamine TEMPOH. This is the crucial reaction step, generating the product (aldehyde). The next steps regenerate the catalyst: rapid syn proportionation of TEMPOH with $TEMPO^+$ regenerates TEMPO; finally, Cu(II) is regenerated by dioxygen, in a process that consumes protons and gives Cu(II) and water. The net reaction is alcohol oxidation by dioxygen to afford aldehyde and water. Importantly, in this catalytic sequence, the actual oxidant is an oxoammonium ion ($TEMPO^+$). In fact, the oxidation of an alcohol in the absence of Cu(II) by using preformed oxoammonium ion, generated electrochemically or with a stoichiometric amount of a primary oxidant, is well-known.[17] In basic solutions where an alcoholate can be formed by deprotonation of the alcohol, the oxidation is usually pictured (see Scheme 2 panels *a* and *b*) as proceeding by a nucleophilic attack at the C−H bond.[4,18] The intermediate alcoholate-oxoammonium complex may either form by bonding of the alcoholate anion to the nitrogen (cf. panel *a*) or to the oxygen (panel *b*). The mechanisms of the oxidation of an alcohol by an oxoammonium ion in basic solution resulting from these pre-complexes have been investigated computationally by Bailey et al.[18] The reported results at the B3LYP/6-31+g* level indicate that attaching the alcoholate to nitrogen at the side of the equatorial methyl substituents yields the clearly preferred pre-complex (in acidic solutions, these authors do not invoke a pre-oxidation complex). We note that the abstraction of the α-hydrogen is pictured in panels *a* and *b* as occurring by nucleophilic attack at the C−H bond. This runs counter to the electrophilic attack we have recently advocated as the mechanism of aliphatic C−H bond hydroxylation in the case of $FeO^{2+}$ and other $MO^{2+}$ [19,20] oxidants. We return to this point below.

**Scheme 2.** Oxidation Mechanisms for H Abstraction from Alcoholate by $TEMPO^+$ Ion[a]



[a] a,b: nucleophilic attack on C−H bond; a′,b′: electrophilic attack on the C−H bond.

Sheldon et al.[16,21] have proposed an alternative mechanism, that differs from the previous one in two respects. They do not consider the oxoammonium ion to be the active agent but rather the TEMPO radical, and they consider the reaction to be Cu-centered in the sense that the TEMPO radical and the alkoxide anion are both in the first coordination sphere of Cu(II), when the abstraction of the α-hydrogen by the O$^\bullet$ of TEMPO takes place. In their proposed reaction cycle (see Scheme 3) the alcoholate coordinates to the copper(II) complex **1** to lead to the alkoxide complex **2**. TEMPO is

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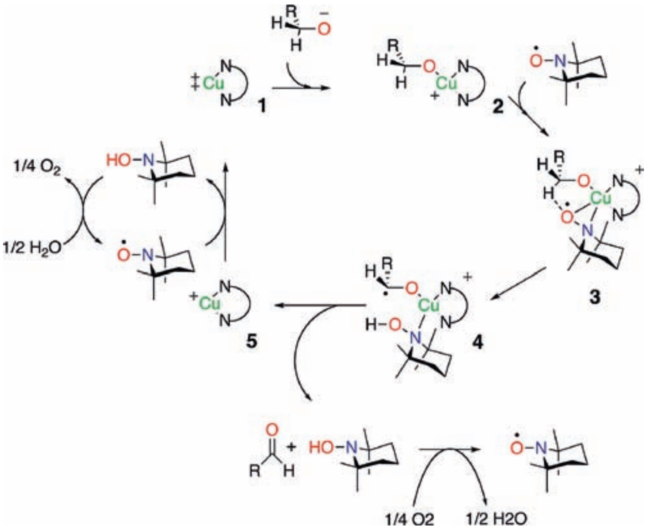
**Scheme 3.** Catalytic Cycle Proposed by Reedijk et al.[21]



thought to coordinate to the copper(II) ion in an $\eta^2$ manner to give (**3**). Support for this coordination of TEMPO radical to the Cu(II) center comes from the work of Caneschi et al.,[22,23] who have interpreted their results as being in agreement with coordination of TEMPO in its radical form. The α-hydrogen would then be transferred to the oxygen atom of TEMPO resulting in a copper complex of TEMPOH and a $\mathrm{RHC^{\bullet}{-}O^{-}}$ radical (**4**). The intramolecular transfer of one electron from the $\mathrm{RHC^{\bullet}{-}O^{-}}$ radical to Cu(II) leads to the aldehyde, TEMPOH and a Cu(I) species (**5**). The initial reagents are then regenerated by the TEMPO-mediated oxidation of Cu(I) to Cu(II), and by the aerobic oxidation of the TEMPOH to TEMPO.

The Sheldon mechanism (also called the radical mechanism) has been supported by Geisslmeir et al.,[5] who have further optimized the reaction conditions for the Cu/TEMPO catalyzed oxidation of alcohols to aldehydes. They note that the higher reactivity of allyl and benzyl alcohols compared to aliphatic alcohols fits in with a radical mechanism, since that mechanism implies the formation of an intermediary radical $\mathrm{RHC^{\bullet}{-}O^{-}}$ that would be more strongly stabilized in the case of allylic and benzylic radicals. The observed diastereomerization of allyl alcohols could be a side reaction of the radical mechanism.[5] Furthermore, according to the literature,[17,24,25] oxoammonium ions of various nitroxyl radicals including TEMPO are rather unstable in aqueous solutions of alkali hydroxides: these compounds are reduced to the nitroxyl radical with simultaneous formation of hydrogen peroxide. This instability of TEMPO$^+$ in basic condition seems to be in conflict with the optimum pH 13 for high reaction rates. These authors[5] therefore favor the reaction with TEMPO in its radical form.

Since many questions concerning the mechanistic details of the Cu-catalyzed oxidation reactions are still open, more insight can be obtained through theoretical investigations. The mechanism of the copper(II)-catalyzed aerobic oxidation of primary alcohols is the subject of this paper. Details regarding the calculations are provided in the Computational Details section. The Results and Discussion section is divided in two parts. First, a preliminary study of the alcohol oxidation in basic conditions (i.e., of the alcoholate) by TEMPO$^+$ without copper is reported. This will highlight that the electronic mechanism is an electrophilic attack on the C−H bond. It brings this C−H bond oxidation by TEMPO$^+$ in line with that by other strong oxidants such as Fenton's reagent (active intermediate FeO$^{2+}$ is strongly electrophilic[19]) and other MO$^{2+}$[20] metal oxides. We will argue that electrophilic attack is probable in view of the fact that the C−H$_\alpha$ bonding orbital in an alcohol is particularly high-lying, so it can donate electrons relatively easily. The antibonding orbital $\sigma^*$(C−H), which would be crucial for a nucleophilic attack, is on the other hand relatively high-lying. Electrophilic attack for C−H bond activation (oxidation) appears to be a general phenomenon. Next the role of the Cu(II)bipy complex in the Cu mediated catalytic reaction is studied. We find that TEMPO coordinates to Cu(II), reducing it to Cu(I) while being oxidized to TEMPO$^+$. The alcoholate also coordinates to the Cu, so the Cu(bipy) complex acts as a template bringing the reactants alcoholate and TEMPO$^+$ in close proximity, and actually, we will see, in good orientation for the H transfer to take place. In this setting, the barrier for the H-bond breaking proves to be a record low. We will also study the selectivity of the reaction with respect to primary versus secondary alcohols. The present reaction has some analogy to the Meerwein−Ponndorf−Verley reduction, or Oppenauer Oxidation, which uses Al(OR)$_3$ as catalyst, but we will not investigate this connection in the present paper.

## Computational Details

Density-functional theory (DFT) calculations were performed using the ADF (Amsterdam Density Functional) package 2007.1[26−28] with a basis set of Slater type orbitals of TZP quality for all atoms. The inner core orbitals (up to 3p for Cu, 1s for C, N, and O) were treated by the frozen core approximation. Relativistic effects were included by using the Zero-Order Regular Approximation (ZORA).[29] All calculations were performed in the spin-unrestricted approach using the OPBE functional, a combination of the OPTX and the PBE functionals.[30,31] OPBE has been shown to yield spin state relative stabilities comparable to hybrid and *meta*-GGA functionals.[32,33] Convergence criteria for geometry optimization were $1 \times 10^{-3}$ hartree in the total energy, $5 \times 10^{-4}$ hartree/Å in the gradients, $1 \times 10^{-2}$ Å in bond lengths, and 0.20° in bond and dihedral angles. When needed, the frequencies are computed analytically. All the transition state (TS)

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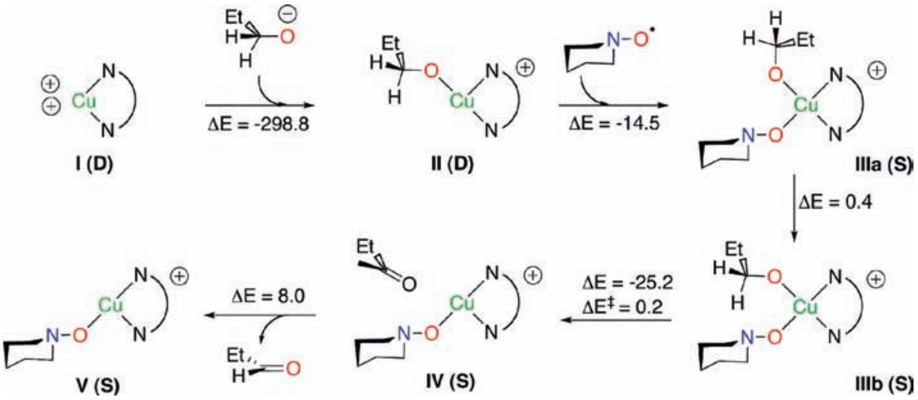
**Scheme 4.** Pathway from Compound **I** to Compound **V**[a]



[a] Energies are given in kcal/mol. (**S**) stands for singlet ground state and (**D**) for doublet ground state.

structures have been characterized by the presence of a single imaginary frequency.

## Results and Discussion

Primary alcohols can be oxidized selectively to the corresponding aldehydes at room temperature with air in $CH_3CN/H_2O$ (2/1) using a [$CuBr_2$(bipy)] complex as catalyst (bipy = 2,2′-bipyridine) and 2,2,6,6-tetramethylpiperidinyl-1-oxy (TEMPO) and a base ($^t$BuOK) as cocatalysts (see Scheme 1).[15,21]

This reaction is a two-electron oxidative process (two H atoms are abstracted from the alcohol) using $O_2$ as a stoichiometric oxidant. The importance of each reactant (catalyst and cocatalysts) is illustrated in Table 1 on the benzyl acohol to benzaldehyde reaction. The presence of TEMPO is essential. Without it, no reaction can be observed (entry 2). As already stated before,[21] the use of an N-donor ligand for the Cu(II) greatly enhances reactivity. Only 6% of benzyl alcohol is converted into benzaldehyde in the absence of bipy in 1.5 h whereas 83% is converted in the presence of bipy within the same duration (entries 1 and 6). Given the formation of complexes of bipy with Cu(II), this already suggests that the coordination environment of Cu(II) is important for the reaction. The second cocatalyst ($^t$BuOK) is optional. Without any base, the [$CuBr_2$(bipy)]-TEMPO catalytic system is active, but 24 h are required for a total conversion instead of 2.5 h in the presence of $^t$BuOK (entries 3, 4, and 6). Such a basic cocatalyst can deprotonate the alcohol and thus favors the coordination of the resulting alcoholate to the copper cation, again suggesting that the reaction is Cu centered.

To explore the possible pathways of the oxidation of primary alcohols, we have performed DFT calculations in the gas phase. TEMPO has been simplified by replacing the four methyl groups by hydrogen atoms in some calculations, when a reduction of the CPU time is needed. Propanol has been chosen as a prototype substrate which allows to distinguish between primary (propan-1-ol, denoted PrOH further on) and secondary (propan-2-ol, denoted iPrOH further on) alcohols. On the basis of our calculations, we can propose the mechanism depicted in Scheme 4 in the case of PrOH. First, in the experimental conditions described previously, $Cu^{2+}$ is coordinated by bipyridine (bipy) leading to compound **I**. The usage of a strong base such as $^t$BuOK ensures the alcohol deprotonation. The resulting alcoholate coordinates strongly to copper (**II**, $\Delta E = -298.8$ kcal/mol). This is not pure energy gain, since the alcoholate will have to displace another ligand such as $Br^-$ or $OH^-$. Moreover, this energy will be different in a solvent, since the solvation energy of the two ions will be larger than that of the final complex. We have verified with a COSMO calculation[34,35] with a dielectric constant of acetonitrile that this coordination energy reduces to $\Delta E = -72.1$ kcal/mol. The neutral TEMPO coordinates less strongly, binding to bare $[Cu(bipy)]^{2+}$ with a $\Delta E$ of $-76.8$ kcal/mol (singlet state), and to $[Cu(bipy)PrO]^+$ with $\Delta E = -14.5$ kcal/mol; with solvent effects the last number changes to $-38.2$ kcal/mol. In **III**, the copper cation holds both the reactants, namely, the alcohol (in its deprotonated form) and TEMPO, in its coordination sphere. This complex is the reactive species: we find that the TEMPO ligand abstracts an α hydrogen of the alcoholate ligand extremely easily (activation energy of only $\Delta E^{\ddagger} = +0.2$ kcal/mol) with respect to conformer **IIIb** (the difference between conformers **IIIa** and **IIIb** will be discussed below). The reaction product is complex **IV**, which is downhill with respect to **III** by $-25.2$ kcal/mol, cf. Scheme 4. Complex **IV** presents the corresponding aldehyde weakly coordinated to the $[Cu(bipy)TEMPOH]^+$ complex. Its dissociation gives the complex **V** and the expected aldehyde ($\Delta E = +8.0$ kcal/mol).

A crucial finding is that the coordination of TEMPO to the Cu(II) center reduces it to Cu(I), forming $TEMPO^+$. The unpaired electron of the TEMPO radical, which resides in an N−O $\pi^*$ antibonding orbital, the highest occupied orbital of TEMPO, goes into the d hole of the $d^9$ Cu(II), forming $d^{10}$ Cu(I). This gives to the Cu(II) indeed the role of oxidizing TEMPO to the oxoammonium ion as postulated by Semmelhack, but at the same time the coordination of the reactants to Cu(I) proves the Sheldon assumption (that the reaction is Cu centered) to be right. We do not find evidence for a TEMPO radical coordination to Cu(II). We will discuss this and other points concerning the Cu complex and the reaction at the Cu center below. To prepare for this, and in view of the important role of $TEMPO^+$, however, we will first revisit alcohol oxidation in basic conditions (i.e., in alcoholate form) by bare $TEMPO^+$, with reference to the work by Bailey et al.[18]

**Alcohol Oxidation with TEMPO in Basic Conditions without the $Cu(bipy)^{2+}$ Catalyst.** We are using in this part

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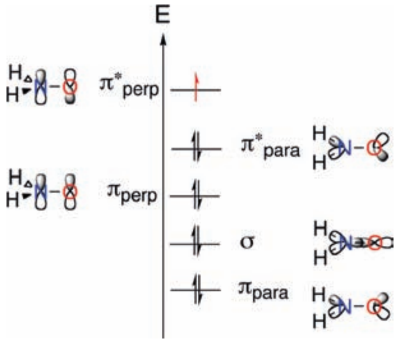
**Scheme 5.** Molecular Orbitals of $H_2NO^+$ and $H_2NO^\bullet$ Resulting from the 1s Atomic Orbitals of the Hydrogen Atoms and Mainly the 2p Atomic Orbitals of the Nitrogen and Oxygen Atoms[a]



[a] The extra unpaired electron of $H_2NO^\bullet$ is represented in red.

of our study the same model as Bailey et al.:[18] the alcohol has been deprotonated into its corresponding alcoholate to mimic the basic conditions and the TEMPO radical is oxidized to $TEMPO^+$. In the following, we present our results and a detailed discussion of the C−H bond breaking occurring during this oxidation reaction.

The electronic structure of $TEMPO^+$ can be easily understood with reference to the orbitals in the prototype nitroxyl radical $H_2NO^\bullet$ and the cation $H_2NO^+$. As illustrated in Scheme 5, the occupied molecular orbitals of the planar $H_2NO^+$ are as follows:

- the $\sigma$(NO)
- two $\pi$ orbitals: the most stable $\pi_{para}$ lies in the plane of the molecule, the less stable $\pi_{perp}$ is perpendicular to the plane.
- the $\pi^*_{para}$ orbital, lying in the plane of the molecule

The lowest unoccupied molecular orbital (LUMO) of the $H_2NO^+$ is the $\pi^*_{perp}$ orbital, perpendicular to the plane of the $H_2NO^+$ molecule. The dihedral angle NOHH is equal to zero to minimize the energy of the $\pi_{para}$ orbital lying in the plane. When adding an electron, we obtain the radical $H_2NO^\bullet$. The dihedral angle NOHH is increasing from 0° to 10° to relax the energy of the $\pi^*_{perp}$ singly occupied molecular orbital (SOMO). This simple orbital scheme is also representative of the electronic structure of $TEMPO^+$ and TEMPO and the same geometrical evolution is observed: the NOCC angle increases from 0° to 10° when an electron is added to the LUMO of $TEMPO^+$. This geometrical parameter is sometimes used as a probe of the electronic nature of TEMPO: radical or cation. We will use it later for Cu coordinated $TEMPO^+$.

Clearly, the pre-oxidation of TEMPO into $TEMPO^+$ enhances its electrophilicity: removing an electron from the SOMO of the TEMPO radical makes the $\pi^*_{perp}$ acceptor orbital particularly low in energy (from −4.9 eV in TEMPO to −9.1 eV in $TEMPO^+$ using the exchange-correlation functional OPBE). The electrophilic nature of $TEMPO^+$ is important. We have stressed before[19,20,36] that some well-known hydroxylation catalysts, such as the Fenton catalyst in abiotic non-heme iron catalyzed oxidation, as well as the porphyrin based ironoxo catalysts in biological chemistry, act by electrophilic attack on C−H bonds. This is in contrast to many reactions where bonds are broken by electron donation by a base into an antibonding orbital, as in the prototypical $S_N2$ reaction where the $\sigma^*$(C−X) bond is attacked by a nucleophile. C−H bonds, however, are relatively high lying and therefore better accessible for electrophiles with low-lying acceptor orbitals, see the comparison in Figure 1 with other A−H bonds. Going through the series of A−H bonds with A = F, O, N, C in the elementary hydrides $AH_n$, we see the $\sigma$(A−H) orbital energies increase considerably at every step. Going to the alcohol, we note there is a particularly large jump in going from $CH_4$ to $CH_3OH$, because of the strong antibonding of the $\sigma(C-H_\alpha)$ with an O lone-pair orbital, cf. Figure 2. The $\sigma$(C−H) orbital is, on the other hand, relatively high-lying, although for the $\sigma$ orbital energies the differences are less striking. The C−H bond is thus relatively sensitive to electrophilic attack, and insensitive to nucleophilic attack. This has been highlighted for metaloxo species as attacking electrophiles before.[19,20,36]

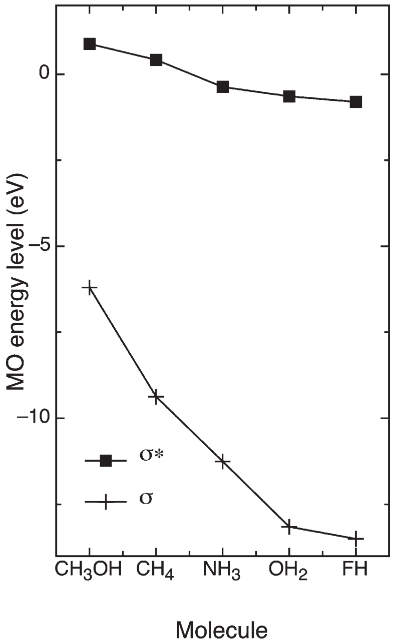


**Figure 1.** Orbital energies for the $\sigma$(A−H) bond orbitals and for the $\sigma^*$(A−H) antibonding orbitals in a series of simple first row hydrides.

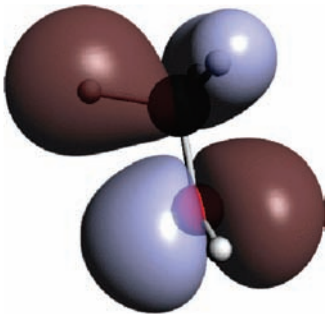


**Figure 2.** HOMO of methanol, an antibonding combination of the C−H bonding orbitals and the O lone pair. As a result this is a relatively high-lying orbital with a large C−H bond contribution.

The $TEMPO^+$ LUMO orbital can accept electron density from the $\sigma$(C−H) at two different atoms: at the oxygen (O-pathway, cf. *a* and *a′* in Scheme 2) and at the nitrogen (N-pathway, cf. *b* and *b′* in Scheme 2). The

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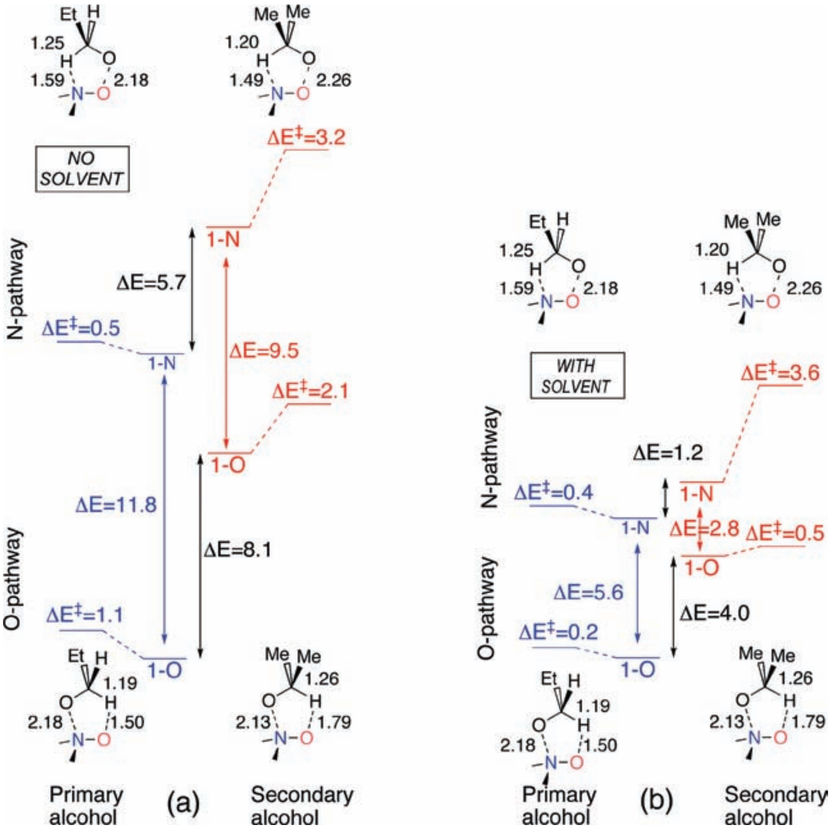
(36) Bernasconi, L.; Louwerse, M. J.; Baerends, E. J. *Eur. J. Inorg. Chem.* **2007**, 3023–3033.

**Scheme 6.** Two Possible Pathways for Alcohol Oxidation by TEMPO$^+$ in Basic Conditions: the **N-pathway** (pre-complex 1-N) and the **O-pathway** (pre-complex 1-O)[a]



[a] Scheme (a) is without solvent (gas phase calculations); scheme (b) is with solvent effects included at COSMO level, dielectric constant of acetonitrile. To the left in each scheme (blue) the alcoholate is propan-1-olate (PrO$^-$, primary). To the right (red) the alcoholate is the propan-2-olate (iPrO$^-$, secondary). Energies are given in kcal/mol. The key distances of the TS structures are given in Å: the C−H distance in both pathways, the O···O and H···N distances in the **N-pathway**, the O···N and the H···O distances in the **O-pathway**.

arrows in panels *a* and *b* are according to the conventional picture,[4,18] indicating a nucleophilic attack on C−H$_\alpha$, while panels *a*′ and *b*′ depict an electrophilic attack. In TEMPO$^+$, the $\pi$* LUMO is 45% on the nitrogen, 40% on the oxygen, which does not allow to make a prediction of the preferred path. It is clear, however, that during the first step of the alkoxide oxidation by TEMPO$^+$, the alkoxide approaches it from the side of the equatorial methyls of this oxoammonium cation to minimize steric repulsion. The alcoholate then binds to TEMPO$^+$ in one of two possible pre-complexes. In the first (**1-O**) the orientation is as in *a* and *a*′ of Scheme 2, with C−H$_\alpha$−O-(TEMPO) bonding and O$^-$(alkoxide)−N(TEMPO) bonding, respectively. In the other pre-complex (**1-N**, cf *b*,*b*′ in Scheme 2) the alcoholate is rotated over 180°, so there are now C−H$_\alpha$−N(TEMPO) and O(alkoxide)−O-(TEMPO) contacts.

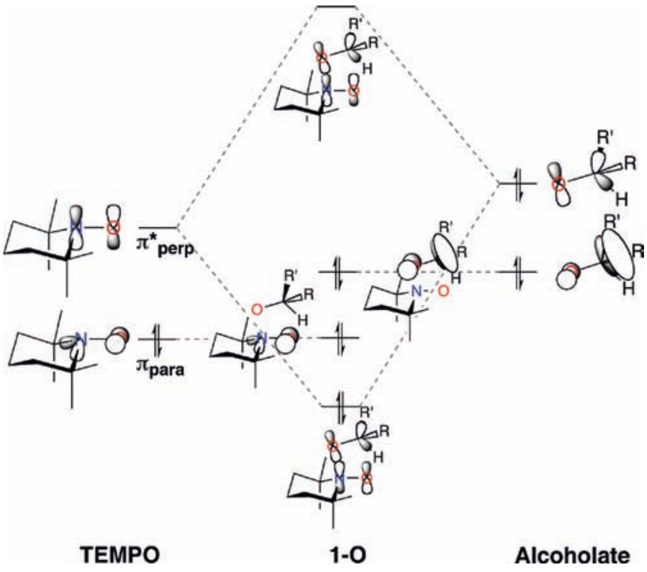
We first discuss the results that have been obtained without solvent effects (gas phase calculations), see Scheme 6a. The pre-complex **1-O** is more stable than the pre-complex **1-N**: **1-O** binds more strongly by 11.8 kcal/mol for PrO$^-$ and by 9.5 kcal/mol for iPrO$^-$ (see Scheme 6). One reason for this stronger bonding is the larger electrostatic interaction in **1-O**. One can easily understand the origin: in TEMPO$^+$, the Mulliken charge on nitrogen is large and positive (+0.51) while it is negative on the oxygen atom (−0.27). In the pre-complex **1-O**, the negative oxygen atom of the alcoholate points toward the positive nitrogen of TEMPO$^+$ whereas this negative atom points toward the negative TEMPO$^+$ oxygen atom in the pre-complex **1-N**. Thus, as shown in Table 2, the electrostatic interactions in **1-O** (−162 kcal/mol (PrO$^-$) and −150 kcal/mol (iPrO$^-$)) are much stronger than in **1-N** (−104 kcal/mol (PrO$^-$) and −94 kcal/mol (iPrO$^-$)). According to Table 2 also the orbital interaction is considerably stronger for **1-O** (−137 kcal/mol for PrO$^-$ and −128 kcal/mol for iPrO$^-$) than for **1-N** (−105 kcal/mol for PrO$^-$ and −92 kcal/mol for iPrO$^-$). In both pre-complexes, **1-O** and **1-N**, the $\pi^*_{\mathrm{perp}}$ orbital of the TEMPO$^+$, which is a $\pi$* antibonding orbital over the N−O bond, interacts with the two lobes of the highest occupied orbital of the alcoholate, which is also a $\pi$ antibonding orbital, over the C−O bond of the alcoholate, cf. Figure 2. A strongly bonding orbital results, see the strong interaction between these two sideways interacting $\pi$* orbitals in the molecular orbital interaction diagram of Scheme 7. The net effect is that in the pre-complexes almost one electron (0.8 el.) is transferred to the TEMPO$^+$ LUMO. Typically, when the attractive terms are large, the Pauli repulsion term is also large (usually because of the shorter distance to which the attractive terms pull the fragments together), and the larger Pauli repulsion in **1-O** counteracts much of the favorable attractive terms. The net balance is the clearly larger stability of **1-O**.

**Table 2.** Decomposition of the Bonding Energy between TEMPO$^+$ and Primary (PrO$^-$) or Secondary (iPrO$^-$) Alcoholate, in kcal/mol[a]

| | | Pauli repulsion | electrostatic interaction | total steric interaction | total orbital interaction | $\Delta E_{prep}$ | $\Delta E$ (total) | $\Delta E_{solv}$ (total) |
|---|---|---|---|---|---|---|---|---|
| **1-O** | PrOH | 146 | −162 | −16 | −137 | 23 | −129.8 | −16.5 |
| **TS 1-O** | PrOH | 114 | −135 | −22 | −127 | 20 | −128.7 | −16.3 |
| **1-O** | iPrOH | 132 | −150 | −19 | −128 | 25 | −121.8 | −12.5 |
| **TS 1-O** | iPrOH | 102 | −120 | −18 | −126 | 24 | −121.3 | −13.0 |
| **1-N** | PrOH | 77 | −104 | −26 | −105 | 13 | −118.0 | −11.0 |
| **TS 1**-N | PrOH | 105 | −126 | −21 | −125 | 27 | −117.0 | −10.6 |
| **1-N** | iPrOH | 63 | −94 | −31 | −92 | 11 | −112.3 | −9.7 |
| **TS 1-N** | iPrOH | 80 | −106 | −26 | −108 | 25 | −109.1 | −6.1 |

[a] $\Delta E_{prep}$ is the energy difference between the free fragments and the prepared fragments (deformed to the geometries they have in the various complexes). Total steric interaction is sum of Pauli repulsion and Electrostatic Interaction. $\Delta E = \Delta E_{prep}$ + total steric interaction + total orbital interaction. $\Delta E_{solv}$(total) is the same quantity with solvent effects included at the COSMO level, dielectric constant of acetonitrile.

**Scheme 7.** Molecular Diagram of **1-O** Resulting from the Interactions between the TEMPO$^+$ Molecular Orbitals and the Alcoholate Molecular Orbitals



In the second step, the α-hydrogen is abstracted as a hydride (H$^-$), leading to the neutral TEMPOH and the expected aldehyde or ketone. Naturally, **1-O** is the precursor of the abstraction by the TEMPO oxygen atom (O-pathway) and **1-N** is the precursor of the N-pathway. We stress that TEMPO$^+$ is acting as an electrophile, therefore the arrows in Scheme 2 should be as in *a′* and *b′*, not as in the conventional diagrams *a* and *b*. The action of TEMPO$^+$ as electrophile is fully analogous to the one of the well-known active oxidative species FeO$^{2+}$ in the Fenton reaction,[19] and in P450 enzymes.[37]

The two pathways are qualitatively very similar. The large electronic donation is made possible by the pre-oxidation of TEMPO into TEMPO$^+$ which increases the electrophilicity of the NO entity. This electronic donation occurs in both pathways. The pathways are depicted in Scheme 6, where also the TS geometries are given. The activation barriers are small (0.5−3.2 kcal/mol). The O-pathway is more favorable, mainly because the pre-complex **1-O** is more stable than the pre-complex **1-N**: **1-O** is stabilized by 11.8 kcal/mol for PrO$^-$ and by 9.5 kcal/mol for iPrO$^-$. This has already been pointed out by Bailey et al.[18]

An important issue is the selectivity toward primary versus secondary alcohols in each case. In the O-pathway, the pre-complex is more stable for PrO$^-$ than for iPrO$^-$ by 8.1 kcal/mol, see Scheme 6, while the H-abstraction barriers are similar for the primary and the secondary alcohol ($\Delta E^{\ddagger}$(PrO$^-$) = 1.1 kcal/mol and $\Delta E^{\ddagger}$(iPrO$^-$) = 2.1 kcal/mol). The greater reactivity of primary alcohols therefore lies essentially in the extra stabilization of the pre-complex for the primary alcohol in the preferred O-pathway. Since the N-pathway is much less likely, the difference between primary and secondary alcohols in that pathway is less relevant, but we note that also in that case the pre-complex is more stable for PrO$^-$ than for iPrO$^-$ (by 5.7 kcal/mol) and the H-abstraction barrier is clearly larger for iPrO$^-$ (3.2 kcal/mol) than for PrO$^-$ (0.5 kcal/mol). So both pathways are selective toward the conversion of primary alcohols. In the O-pathway the selectivity is provided by the relative stabilization of the pre-complex whereas in the N-pathway the selectivity is also provided by the differentiated H-abstraction barriers.

Although the complexation energy of the two ionic moieties, alcoholate and TEMPO$^+$, will be very different in solvent from gas phase, the effect of solvent is not expected to affect the reaction mechanism essentially. There will be of course quantitative differences. We have repeated all of the calculations with solvent effects included at the COSMO level,[34,35] using the dielectric constant of acetonitrile. As can be seen in Scheme 6b, there are significant quantitative differences in for instance the relative energies of the **1-O** with respect to the **1-N** conformations of the complex: for both primary and secondary alcohol the gap is reduced considerably (from 11.8 to 5.6 for primary alcohol, from 9.5 to 2.8 kcal/mol for secondary alcohol). This is consistent with our identification of the electrostatic interaction as the most important factor in the preference for **1-O**; this effect is reduced in the solvent. The relative order of all species, however, remains the same, and the various transition barriers are less affected. The TS barriers of the **1-N** species change little, both for primary and secondary alcohol, the barriers for **1-O**, which were already small (1.1 and 2.1 kcal/mol respectively) reduce even further, to 0.2 and 0.5 kcal/mol, respectively. The selectivity for primary alcohol, which is not strong in our calculations, should be caused by the larger stability of the **1-O** pre-complex for the primary alcohol, as in the gas phase calculations.

**Alcohol Oxidation with TEMPO in Basic Conditions with the Cu(bipy)$^{2+}$ Catalyst.** When Cu(bipy)$^{2+}$ is present,

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(37) Shaik, S.; Kumar, D.; de Visser, S. P.; Altun, A.; Thiel, W. *Chem. Rev.* **2005**, *105*, 2279–2328.

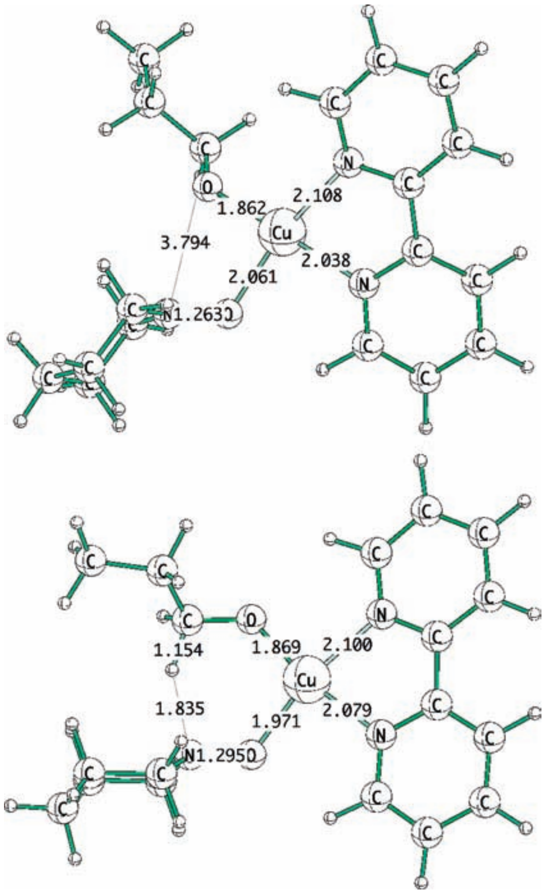


**Figure 3.** Optimized structure of compound **IIIa** (upper panel) and of compound **IIIb** (lower panel).

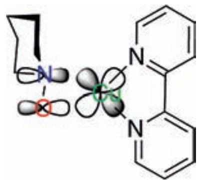
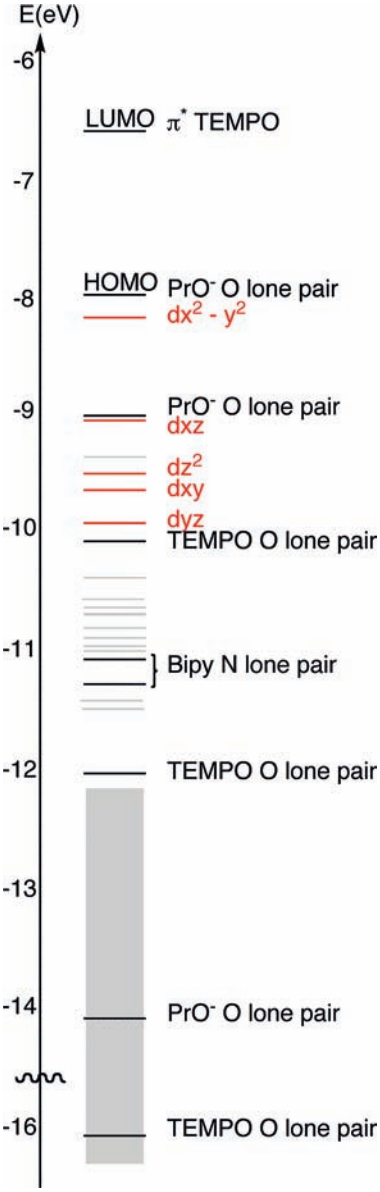


**Figure 4.** Doubly occupied bonding orbital $d_{x^2-y^2} + \pi^*$ which can orient the N−O bond in the plane of the square planar coordination if there are only two other ligands (the two N lone pairs of bipyridine in our case). This is not the lowest energy coordination in this case.

we have already noted that both the alcoholate and the TEMPO coordinate to Cu to form the key species **III** (see Scheme 4). Using the model of TEMPO with the four methyl substituents omitted, for computational expediency, we have optimized two conformers of **III**, both in a singlet ground state: conformer **IIIa** and conformer **IIIb** (Figure 3). Those two conformers are almost isoenergetic (0.4 kcal/mol), but they exhibit quite different geometries. In both conformers the Cu ion has square planar coordination, two coordination sites being occupied by oxygens of the alcoholate and TEMPO, respectively. At variance with the coordination assumed by Gamez et al.[21] (see Scheme 3), TEMPO does not coordinate to the Cu(II) ion in an $\eta^2$ manner, but end-on $\eta^1$, only through the oxygen atom. The supposedly $\eta^2$ coordination of TEMPO (as radical) to Cu plays an important role in the Sheldon mechanism. Sheldon et al.[16,21] assume this coordination based on the work of Rey et al.[22,23] These authors found an $\eta^2$ coordination of TEMPO in a complex with $CuBr_2$, but $\eta^1$ coordination in a complex with $CuCl_2$. In the $CuBr_2$(TEMPO) complex the Cu ion has approximate square planar coordination, with N and O of TEMPO occupying two sites. In the $CuCl_2$ complex dimerization takes place, resulting in two Cu ions bridged by two $\mu$ $Cl^-$ ions, each Cu ion having an additional $Cl^-$ ligand and TEMPO oxygen to complete the square planar coordination arrangement. Apparently, in both cases there is an approximate square planar surrounding of the Cu ion. So TEMPO can coordinate both in the $\eta^1$ mode, using an oxygen lone pair, and in the $\eta^2$ mode, where its unpaired electron in the $\pi^*$ orbital pairs up with the unpaired electron in the $d_{x^2-y^2}$ orbital of the $Cu(d^9)^{2+}$ to form a doubly occupied orbital, see Figure 4. So what happens depends on the (other) ligands. Apparently, with bromide ligands the $\eta^2$ coordination is realized, whereas with chloride ligands an $\eta^1$ coordination is found, the square planar coordination being achieved by dimerization. In our Cu(bipy)(alcoholate)$^+$ complex, with three coordination sites occupied, an $\eta^2$ coordination of TEMPO cannot be adopted, and it simply coordinates in an $\eta^1$ fashion with an oxygen lone pair at the fourth coordination site. Interestingly, we have found that with only the bipy ligand coordinated to Cu, an $\eta^2$ coordination of TEMPO can be obtained in the calculations, but it is a local minimum. The overall minimum energy is obtained with an $\eta^1$ coordination of TEMPO. We conclude that at Cu(bipy)$^{2+}$ an $\eta^2$ coordination does not occur. Moreover we wish to stress that TEMPO never retains its radical character. In the $\eta^1$ coordination the unpaired electron in the $\pi^*$ orbital moves into the orbital with mostly $d_{x^2-y^2}$ character, formally reducing Cu to $Cu(d^{10})^+$ and leaving the $\pi^*$ empty, that is, generating a TEMPO$^+$ ligand with a $\pi^*$ acceptor orbital. But not even in the $\eta^2$ coordination does the postulated radical character of coordinated TEMPO exist. In the $\eta^2$ configuration (which apparently is the overall minimum in the dibromide Cu(II) complex), an electron pair bond is formed by the $d_{x^2-y^2}$ and the $\pi^*$ orbitals, see Figure 4, where the occupied lower (bonding) orbital will have more $d_{x^2-y^2}$ character, and the unoccupied upper (antibonding) orbital will have more $\pi^*$ character. This is exactly what Rey et al.[22] already found in their Extended Hückel calculations for $Cu(Br)_2$(TEMPO); in agreement with this they found the compound to be diamagnetic. So there simply is a straightforward closed shell situation with a doubly occupied bonding orbital. We have verified that if one does a spin unrestricted calculation and starts with a localized spin up electron on the metal and a spin down electron on the ligand, the calculation yields again two identical spin up and spin down orbitals, both equal to the closed shell bonding orbital obtained in a spin restricted calculation. This is always the case if the overlap (bonding) between the moieties is not very weak. The normal closed shell situation with a doubly occupied bonding orbital should not be described as a TEMPO radical and a $Cu(d^9)^{2+}$ having (very) strong antiferromagnetic interaction.[22,23]

In view of the importance of the electronic structure of the Cu(bipy)(alcoholate)(TEMPO)$^+$ complex, we have performed a detailed electronic structure analysis. In the molecular orbital (MO) level diagram of Scheme 8 it is clear that there are five occupied Cu 3d orbitals (indicated

**Scheme 8.** **IIIb** Molecular Orbital Scheme[a]



[a] Red: the predominantly Cu 3d orbitals; black: coordinating ligand levels of lone pair character on N of bipyridine and O of TEMPO and $PrO^-$; gray: remaining levels with different character like bipy $\pi$ and $\sigma$ orbitals, and TEMPO and alcoholate orbitals.

**Table 3.** Fragment Analysis of Compound **III**[a]

| fragment | 3d (bipy-$Cu^+$) | LUMO ($TEMPO^+$) | HOMO ($PrO^-$) |
|---|---|---|---|
| **IIIa** | 9.40 | 0.80 | 1.90 |
| **IIIb** | 9.35 | 1.10 | 1.50 |
| **IIIb** without $PrO^-$ | 9.35 | 0.65 | |
| **IIIb** without $TEMPO^+$ | 9.82 | | 1.80 |

[a] The three fragments are the closed shell fragments $Cu^+$, $TEMPO^+$, and $PrO^-$. The gross populations of the relevant fragment molecular orbitals are given: the 3d population of the copper cation, the LUMO population of the $TEMPO^+$, and the HOMO population of the alcoholate $PrO^-$.

in red). This is in agreement with the fact that we postulate Cu to have a $d^{10}$ configuration. Of course the red levels do not have 100% 3d character, but they are mostly 3d and should be identified as the Cu 3d levels. The $d_{x^2-y^2}$ is clearly the highest d level, as expected in a square planar environment, but it is still in the occupied space and therefore (nominally) doubly occupied. We also find in the upper part of the occupied space the lone pairs belonging to the N atoms of the bipy and to the oxygen atoms of the alcoholate and TEMPO, which provide the coordination of the ligands to the Cu ion. The LUMO is the $\pi^*$ of the TEMPO, which has lost its electron to the $d_{x^2-y^2}$. The Mulliken orbital populations in Table 3 substantiate this picture. Using as molecular fragments the closed shell systems $Cu^+$, bipy, $TEMPO^+$, and $PrO^-$, we can obtain the Mulliken orbital populations of the Cu atomic orbitals (AOs) and of the MOs of the other fragments. In all complexes, the 3d population is close to 10 (between 9.40 and 9.80). The Mulliken charge on copper is around +0.8. So, in these species, the degree of oxidation of copper is indeed closer to +I than to +II: copper has been reduced. The LUMO of $TEMPO^+$ is low-lying and therefore mixes considerably with the occupied orbitals, acquiring already a substantial population of 0.65 el. if the alcoholate is not yet coordinated. In conformation **IIIb** (Figure 3), where the $C-H_\alpha$ of the alcoholate can donate to the $TEMPO^+$ LUMO, the population of the latter increasing to 1.10.

We will next discuss how the effects of the complexation on the electronic and geometric structure lead to high efficiency and high selectivity of the H abstraction reaction.

**High Efficiency.** The simultaneous presence of the alcoholate and TEMPO ligands in **III** has interesting effects on the geometry and electronic structure of the complex. Figure 3 upper panel (conformer **IIIa**) and lower panel (conformer **IIIb**) show that in both conformations the ring of the TEMPO moiety is perpendicular to the coordination plane, and thus the empty $\pi^*$ orbital is lying in that plane. The important difference between the two conformers **IIIa** and **IIIb** lies in the arrangement of the aliphatic alcohol chain with respect to the TEMPO molecule, and in the TEMPO nitrogen environment. In the conformer **IIIa**, the chain minimizes its steric interactions with TEMPO. The $H_\alpha$'s are not close to TEMPO, the distance between the TEMPO and the closest $H_\alpha$ is long: $N-H_\alpha = 3.79$ Å; $O-H_\alpha = 3.77$ Å. In the other conformer (**IIIb**), only 0.4 kcal/mol higher in energy, one of the two C−H bonds in α position lies in the plane of the square planar complex and points directly to the TEMPO. The distance is much shorter, in particular to the nitrogen: $N-H_\alpha = 1.84$ Å; $O-H_\alpha = 2.45$ Å. In this conformation there is significant electronic donation from the $\sigma$(C−H) orbital into the LUMO of the $TEMPO^+$ fragment, the $\pi^*_{\text{perp}}$(NO) orbital. Rotation of the C−H bond toward the NO moiety of the TEMPO ligand (**IIIa** → **IIIb**) induces an electronic donation from the HOMO of $PrO^-$ (population drops from 1.90 to 1.50) into the acceptor $\pi^*_{\text{perp}}$(NO) orbital (population rises from 0.80 to 1.10). This intramolecular complex formation between the $PrO^-$ and $TEMPO^+$ ligands can also be traced in the **IIIb** molecular orbitals: in the HOMO-2 orbital of **IIIb**, which is the antibonding combination of the O lone pair and $C-H_\alpha$ of $PrO^-$, there is a clearly visible admixture in a bonding way of the $\pi^*_{\text{perp}}$(NO) orbital of $TEMPO^+$ (see Figure 5, lower panel). This accounts for the increase of population of the $\pi^*$ orbital.

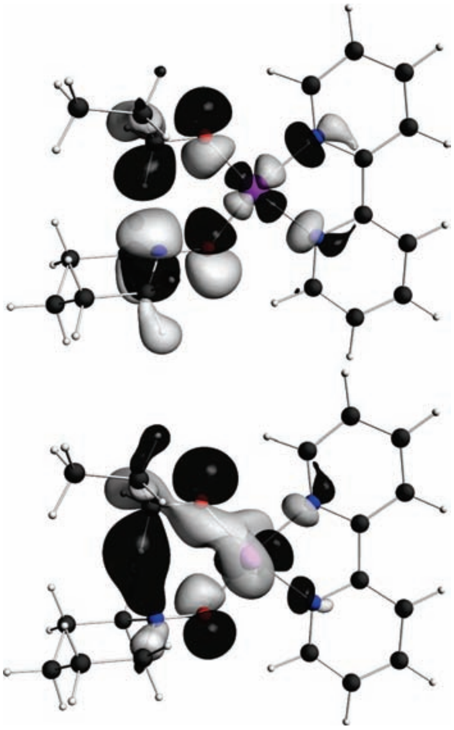


**Figure 5.** Relevant MO of **IIIb**: LUMO (top) and HOMO-2 (bottom).

**Table 4.** Nitrogen Pyramidalization in Some Key Compounds Given by the NOCC or NOHH Dihedral Angle (in deg)

| species | | | dihedral angle |
|---|---|---|---|
| $H_2NO^+$ | | | 0 |
| $H_2NO$ | | | 10 |
| $TEMPO^+$ | | | 0 |
| TEMPO | | | 11 |
| **IIIa** | TEMPO model | PrOH | 3 |
| **IIIa** | TEMPO model | iPrOH | 1 |
| **IIIa** | TEMPO | PrOH | 0 |
| **IIIa** | TEMPO | iPrOH | 0 |
| **IIIb** | TEMPO model | PrOH | 25 |
| **IIIb** | TEMPO model | iPrOH | 27 |
| **IIIb** | TEMPO | PrOH | 14 |
| **IIIb** | TEMPO | iPrOH | 12 |

The $\pi^*_{\text{perp}}$(NO) orbital of $TEMPO^+$ on the other hand, is pushed up by antibonding with the $PrO^-$ HOMO, as is clearly visible in Figure 5, upper panel. These panels also demonstrate that the levels in Scheme 8 are not purely $TEMPO^+$ LUMO ($\pi^*$) or $PrO^-$ HOMO ($O^-$ lone pair/ $C-H_\alpha$) orbitals, but are the mixtures pictured in Figure 5. This orbital mixing also shows up in the umbrella like conformation at N of $TEMPO^+$ in **IIIb**, whereas it is almost planar in **IIIa** (the NOCC dihedral angle is much greater in **IIIb** than in **IIIa**: 25° vs 3°), cf. Table 4. The planar conformation in **IIIa** around N indicates, as we have seen, that the ligand is the $TEMPO^+$ ion, while the umbrella conformation around N in **IIIb** indicates donation out of the $C-H_\alpha$ bond to the $\pi^*$ orbital of $TEMPO^+$. The pyramidalization at the N of TEMPO diminishes the N$-$O antibonding in the $\pi^*$ orbital, hence lowers the $\pi^*$ orbital so that it can interact better with the $C-H_\alpha$ donor orbital. In summary, the coordination to Cu of the alcoholate and the $TEMPO^+$ locks them in close proximity so they can form the complex bond between the $C-H_\alpha$ donor orbital and the $\pi$ orbital at N of $TEMPO^+$ that we already observed in the case of the N-pathway in the free molecules.

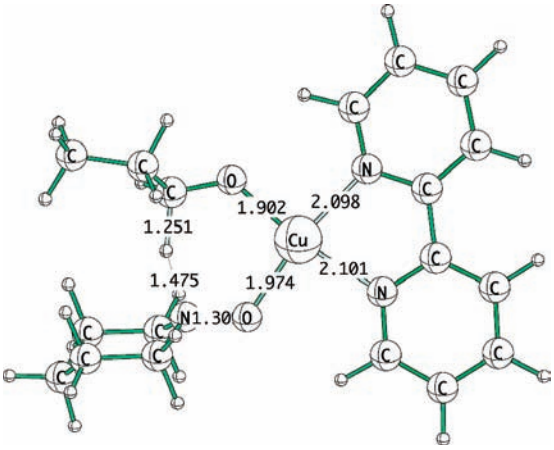


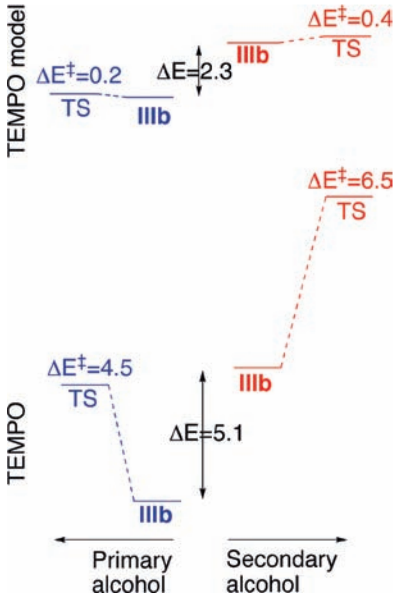
**Figure 6.** TS structure of the **III**→**IV** step.

The $H_\alpha$ abstraction can now occur in the **IIIb** conformation as an intramolecular reaction, the **IIIb** → **IV** step (Scheme 4: the $H_\alpha$ is abstracted by the TEMPO *nitrogen*). In the resulting product **IV**, the aldehyde is already formed and is not coordinated anymore to copper. This process is exothermic by −25.5 kcal/mol. The TS structure is depicted in Figure 6, and the calculated activation energy is about 0.2 kcal/mol. To our knowledge this is the lowest barrier ever found for a C$-$H bond breaking. Clearly, $Cu^{2+}$ by complexing the TEMPO and the alcoholate, plays an important electronic and template function: (1) it oxidizes TEMPO into $TEMPO^+$, resulting into an activated acceptor orbital; (2) it accommodates the alcoholate in such a configuration that the C$-$H bond to be broken points toward the $TEMPO^+$ acceptor orbital and thus already partially transfers electronic density. This is the reason why the H-abstraction barrier is so low.

**High Selectivity.** To understand the high selectivity of this catalytic system in favor of primary alcohols, we compare the H-abstraction step for both a primary and a secondary alcohol. As before, we have chosen the propan-1-ol (PrOH) as the primary alcohol and the propan-2-ol (iPrOH) as the seconday alcohol.

Employing the model of TEMPO used until now, with the four methyl substituents omitted, we have first calculated the analogous complexes and TS for iPrOH. The intermediate **IIIb** exhibits the same nitrogen pyramidalization: NOCC is even larger when we use iPrOH than when we use PrOH as a substrate (27° vs 25°, see Table 4). Indeed, the $\sigma$(C$-$H) is again strongly donating electronic density into the $\pi^*_{\text{perp}}$ orbital of the NO entity. As a consequence, the activation barrier for the **IIIb**→**IV** step is also dramatically low when we use the secondary alcohol as a substrate ($\Delta E^\ddagger$ = +0.4 kcal/mol). So we cannot explain the great selectivity toward primary alcohols of this system using this limited model for TEMPO. Moreover, from a thermodynamic point of view, the $H_\alpha$ of a secondary alcohol should be easier to abstract than the $H_\alpha$ of a primary alcohol. So we expect that the observed selectivity in favor of the primary alcohol is caused by steric effects. To take them fully into account,

**Scheme 9.** Energy Differences between the **IIIb** Complexes Calculated with Full TEMPO (Lower Panel) and with Model TEMPO (Methyls Replaced by H's, Upper Panel)[a]



[a] The differences are between the primary alcoholate propan-1-olate ($PrO^-$) (blue path, to the left) and the secondary alcoholate propan-2-olate ($iPrO^-$) (red path, to the right). The zero energy is in each case for the free, geometry relaxed closed shell fragments $Cu(bipy)^+$, alcoholate, and $TEMPO^+$. The TS barriers for the H-abstraction step are also given. Energies in kcal/mol.

we have switched to the full TEMPO adding the four methyl groups on the cyclohexane ring.

With the full TEMPO, with the four methyl groups surrounding the NO entity, the steric effects are stronger, and disfavor the secondary alcohol more strongly. The energetic data collected in Scheme 9 show that the formation of the crucial precursor complex **IIIb** is slightly disfavored for the secondary alcohol with the model TEMPO ($\Delta E$ = +2.3 kcal/mol), while with the full TEMPO the bias against the secondary alcohol becomes stronger: $\Delta E$ = +5.1 kcal/mol. Note that the zero energy is in both cases the free fragments $Cu(bipy)^+$, $TEMPO^+$ and alcoholate (primary in one case, secondary in the other case). The fragments are in their geometry relaxed configurations. The difference $\Delta E$ = 5.1 kcal/mol thus denotes the difference in complex formation energy from these geometry relaxed ground state fragments (i.e., stronger for primary than for secondary alcoholate). In agreement with the somewhat weaker complexation energy of the secondary alcoholate, the NOCC dihedral angle in **IIIb** is smaller when the substrate is a secondary alcohol than when it is a primary alcohol (12° vs 14°, see Table 4). We then also expect a greater barrier for secondary alcohols. Indeed, we have obtained a larger barrier for the secondary alcohol than for the primary alcohol ($\Delta E^{\ddagger}$ (iPrOH) = +6.5 kcal/mol versus $\Delta E^{\ddagger}$ (PrOH) = +4.5 kcal/mol). For the model TEMPO the difference between secondary and primary alcohol was only 0.2 kcal/mol (increase from 0.2 to 0.4 kcal/mol), whereas it is 2 kcal/mol for the full TEMPO. The Pauli repulsion due to the methyl groups pointing toward the substrate is responsible for this differentiated complexation energy and activation energy.

The H-abstraction in the pre-complex **IIIb** is analogous to the N-pathway we have discussed previously for the bare $TEMPO^+$ ion. The differences between primary and secondary alcohol are not more pronounced with the Cu complex than with free $TEMPO^+$: the Cu(bipy)(alcoholate)$(TEMPO)^+$ complex is more stable by 5.1 kcal/mol when the alcohol is a primary one, compared to 5.7 kcal/mol preference for primary alcohol in the **1-N** conformation of the complex with free $TEMPO^+$ and 8.1 kcal/mol more favorable for primary alcohol in **1-O**. In the Cu complex the TS is higher in energy for the secondary alcohol than for the primary alcohol in **IIIb** by 7.1 kcal/mol (it was 8.4 kcal/mol lower for the secondary alcohol in the N-pathway, and 9.1 kcal/mol in O-pathway). The selectivity in favor of primary alcohols lies in all cases *both* in a smaller barrier and in a greater stabilization of the pre-complex **IIIb**.

Although in our calculations the reaction is clearly favored for primary alcohols, the difference between primary and secondary alcohols is not as large as in the O-pathway. The calculations thus do not fully account for the high selectivity observed in the experiments, although they do indicate that the origin of the selectivity must be sought in steric effects.

## Conclusions

In this theoretical work, we have investigated the key step of a mild and selective oxidative catalyst recently proposed by Gamez et al.[15] This system provides a nice route to aerobic oxidation of primary alcohols into aldehydes, using $[Cu(bipy)]^{2+}$, the TEMPO radical, and a strong base as the catalytic system.

The most important conclusion of this work is that the action of TEMPO in the catalytic system is completely analogous to that of the well-known oxidant $TEMPO^+$. In fact, the primary action of the Cu complex is to oxidize TEMPO to $TEMPO^+$; with neutral TEMPO (i.e., without the Cu complex) the reaction does not occur. We have demonstrated that the action of $TEMPO^+$, both the free ion in solution and the coordinated $TEMPO^+$, consists of an electrophilic attack by the low-lying LUMO (the N−O antibonding $\pi^*$ orbital) at the $C-H_\alpha$ bond of the alcohol. The mechanism of C−H bond activation and oxidation that we find here is strongly analogous to the one occurring in other oxidative systems such as the ferryl (iron(IV)oxo) ion occurring in much biotic and abiotic oxidation catalysis: the oxidation is by electrophilic attack, the C−H bond breaking being induced by a strong electronic donation from the $\sigma$(C−H) orbital into the lowest acceptor orbital of the catalyst. A wide variety of different oxidation catalysts can thus be understood from the unifying electronic structure viewpoint of electrophilic activation of the C−H bond. We have stressed that C−H bonding orbitals in general are relatively high-lying, compared to other A−H bonding orbitals. In particular this is the case for the $C-H_\alpha$ of an alcohol because of its antibonding with an O lone pair. This makes it particularly susceptible to electrophilic attack.

For the oxidation reaction of bare $TEMPO^+$ we have found two pathways. The O-pathway (abstraction of $H_\alpha$ by the oxygen) appears to be the most likely mechanism, because the **1-O** complex with $C-H_\alpha$ interacting with the O side of the

$\pi^*$ is more stable than the **1-N** complex, whereas the TS barrier is hardly higher (1.1 kcal/mol vs 0.5 kcal/mol). The selectivity toward primary alcohols can be understood from a stronger stabilization of the pre-complex $\mathrm{TEMPO}^+{-}\mathrm{RO}^-$ for primary alcohols; for the **1-O** complex the pre-complex with the primary alcohol PrOH is 8.1 kcal/mol lower than for the secondary alcohol iPrOH. The activation barriers are slightly in favor of the secondary alcohol (1.1. for primary vs 2.1 kcal/mol for secondary alcohol). Indeed, the hydride transfer to the oxygen atom of the $\mathrm{TEMPO}^+$ is almost a barrierless process for both primary and secondary alcohols. Also the barriers for the N-pathway (abstraction of $\mathrm{H}_\alpha$ by the nitrogen of $\mathrm{TEMPO}^+$) are very low (0.5 for primary and 3.2 kcal/mol for secondary alcohol).

In the green procedure proposed by Gamez et al.,[15] the oxidation is not stoichiometric but can be performed with oxygen in a catalytic process with $\mathrm{Cu(bipy)}^{2+}$ and TEMPO as cocatalysts. We find the reaction to take place at the Cu center: Cu can coordinate the alcoholate and the TEMPO through their oxygen atoms. This coordination has an important electronic effect. TEMPO has been previously supposed to be coordinated as a radical and to react as such. We find, however, that TEMPO is oxidized by $\mathrm{Cu(d^9)}^{2+}$ to $\mathrm{TEMPO}^+$ so its lowest acceptor orbital $\pi^*_{\mathrm{perp}}(\mathrm{NO})$ can easily accept electronic donation from the alcoholate HOMO $\sigma(\mathrm{C{-}H})$. Cu becomes $\mathrm{Cu(d^{10})}^+$. The objection raised against the $\mathrm{TEMPO}^+$ ion as reactive intermediate, that it is not stable in strongly basic solution, is not valid here since $\mathrm{TEMPO}^+$ is not present as a free ion in solution. We emphasize that the $\mathrm{Cu(bipy)}^{2+}$ complex acts as a template; it coordinates the alcoholate and the TEMPO in adjacent coordination sites in the equatorial plane, where they can easily form an "intramolecular pre-complex" in which the $\mathrm{C{-}H}_\alpha$ interacts with the $\mathrm{TEMPO}^+$ nitrogen (conformation **IIIb**). The oxidation then follows the analog of the N-pathway of free $\mathrm{TEMPO}^+$. The $\mathrm{Cu(bipy)}^{2+}$ therefore acts both electronically, oxidizing TEMPO to $\mathrm{TEMPO}^+$, and as a template, directing the reactants into suitable position.

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