Mechanism of Electron Transfer Oxidation of 4-Substituted 1-Benzyl-1,4-dihydronicotinamides

Naoki Takada, Shinobu Itoh, and Shunichi Fukuzumi*
Department of Applied Chemistry Faculty of Engineering, Osaka University, Yamadaoka, Suita, Osaka 565

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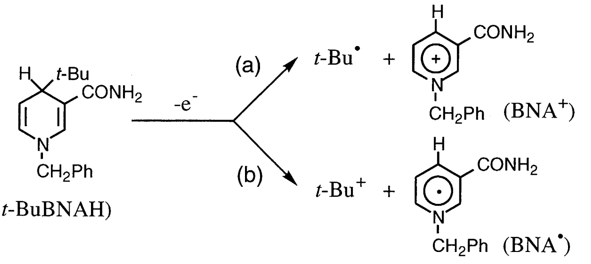
Electron transfer oxidation of variously 4-substituted 1-benzyl-1,4-dihydronicotinamides (RBNAH) by $[Fe(phen)_3]^{3+}$ (phen = 1,10-phenanthroline) results in formation of $RBNAH^{\bullet+}$, followed by cleavage of the C(4)-H or C(4)-C bond of $RBNAH^{\bullet+}$ depending on the substituent R. In particular, the C(4)-C bond cleavage of $t\text{-BuBNAH}^{\bullet+}$ yields exclusively BNA^+ and *tert*-butyl radical ($t\text{-Bu}^\bullet$) which is detected by applying a rapid mixing flow electron spin resonance (ESR) technique.

It has been well established that electron transfer oxidation of an NADH model compound, 1-benzyl-1,4-dihydronicotinamide (BNAH) by various one-electron oxidants results in formation of $BNAH^{\bullet+}$, followed by deprotonation at the 4-position of $BNAH^{\bullet+}$ to yield $BNA^\bullet$ which is further oxidized to BNA^+.[1-3] Recently we have reported that cleavage of the C(9)-C or C(9)-H bond of radical cations of NADH analogs, 9-substituted 10-methyl-9,10-dihydroacridines (AcrHR) occurs in the electron transfer oxidation of AcrHR by Fe^{3+} complexes depending on the substituent R.[4] Savéant et al. have recently reported that the electrochemical oxidation of 4-*tert*-butylated BNAH (*t*-BuBNAH) also results in the C(4)-C bond cleavage rather than deprotonation of $t\text{-BuBNAH}^{\bullet+}$.[5] However, there are two possible modes of the carbon-carbon bond cleavage in such reactions to generate (a) $t\text{-Bu}^\bullet$ and BNA^+ or (b) $t\text{-Bu}^+$ and $BNA^\bullet$ as shown in Scheme 1. It seems difficult to distinguish the two pathways, since $t\text{-Bu}^\bullet$ and $BNA^\bullet$ are further oxidized to $t\text{-Bu}^+$ and BNA^+, yielding the same products irrespective of the cleavage mode.[6,7] We report herein the mechanism of the electron transfer oxidation of a series of 4-alkylated BNAH (RBNAH, R = Et, *i*-Pr, and *t*-Bu) to clarify the cleavage mode of the C(4)-C bond, showing that the selectivity of the C(4)-H or C(4)-C bond of $RBNAH^{\bullet+}$ varies depending on R. The formation of $t\text{-Bu}^\bullet$ (pathway (a) in Scheme 1) rather than $t\text{-Bu}^+$ has successfully been shown by the trap of $t\text{-Bu}^\bullet$ with oxygen to produce $t\text{-BuOO}^\bullet$ which can be detected by ESR.

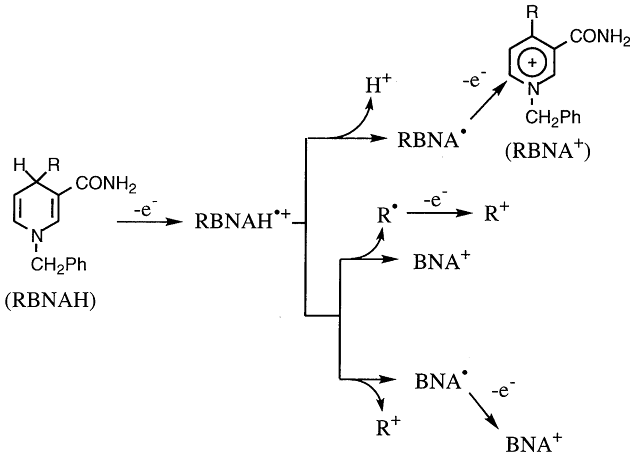
The one-electron oxidation potentials (E^0_{ox} *vs*. SCE) of RBNAH (R = Et, *i*-Pr, and *t*-Bu)[8] have been determined as 0.70-0.72 V by applying a second harmonic ac voltammetry.[9] These oxidation potentials are smaller than the one-electron reduction potential of $[Fe(phen)_3]^{3+}$ as 1.07 V (*vs*. SCE).[10] Thus, electron transfer from RBNAH to $[Fe(phen)_3]^{3+}$ occurs rapidly in MeCN at room temperature as indicated by the instant increase in absorption spectrum of $[Fe(phen)_3]^{2+}$ (λ_{max} = 508 nm). The electron transfer oxidation of RBNAH may result in cleavage of either the C(4)-C or C(4)-H bond of $RBNAH^{\bullet+}$ to yield the two different types of products as shown in Scheme 2, where there are two possible modes of cleavage.



Scheme 1.

The product yields of BNA^+ vs $RBNA^+$ obtained from ^1H NMR are listed in Table 1. The ratio of BNA^+ to $RBNA^+$ varies depending on the substituent R. In the case of *t*-BuBNAH, the C(4)-C bond of *t*-BuBNAH is cleaved exclusively to yield BNA^+ whereas the C(4)-H bond of EtBNAH is cleaved mainly to yield $EtBNA^+$. In the case of *i*-PrBNAH, both the C-H and C-C bonds are cleaved to generate the two different types of products.

The products derived from the alkyl fragmentation are found to be different between the absence and presence of O_2 in the case of *t*-BuBNAH (Table 2). In the absence of O_2, *N*-*tert*-butylacetamide (*t*-BuNHCOMe) was obtained as the main product. This may be attributed to the reaction of $t\text{-Bu}^+$ derived from the C-C bond cleavage with the solvent (MeCN) and residual water.[11] On the contrary, the yield of *tert*-buthanol (*t*-BuOH)



Scheme 2.

Table 1. The product yields of BNA^+ *vs*. $RBNA^+$ for the electron transfer oxidation of RBNAH (5.0×10^{-3} mol dm^{-3}) by $[Fe(phen)_3]^{3+}$ (5.0×10^{-2} mol dm^{-3}) in deaerated MeCN

R	Yield / %	
	BNA^+	$RBNA^+$
tert-butyl	100	0
isopropyl	92	8
ethyl	9	91

Table 2. Product yields of the electron transfer oxidation of t-BuBNAH (5.0×10^{-3} mol dm^{-3}) with $[\mathrm{Fe(phen)_3}]^{3+}$ in MeCN

	$[\mathrm{Fe(phen)_3}]^{3+}$ / mol dm^{-3}	Yield^a / %	
		t-BuNHCOMe	t-BuOH
in the absence of O_2	1.0×10^{-2}	69	29
	2.5×10^{-2}	72	22
in the presence of O_2	1.0×10^{-2}	39	52
	2.5×10^{-2}	48	48

^{a} 2-Methylpropene is also formed as a minor product.

becomes larger than t-BuNHCOMe in the presence of O_2 (Table 2). The stoichiometric ratio of t-BuBNAH to $[\mathrm{Fe(phen)_3}]^{3+}$ (1.0×10^{-4} mol dm^{-3}) was determined from the increase in absorption spectrum of $[\mathrm{Fe(phen)_3}]^{2+}$ in both the absence and presence of O_2. In the absence of O_2, the stoichiometric ratio of t-BuBNAH to $[\mathrm{Fe(phen)_3}]^{3+}$ is 1:2 whereas it is 1:1 in the presence of O_2. This means that no further oxidation of the cleaved product by $[\mathrm{Fe(phen)_3}]^{3+}$ occurs in the presence of O_2 although it is further oxidized in the absence of O_2.

The product analyses and stoichiometries described above suggest that the C-C bond cleavage of RBNAH$^{\bullet+}$ results in formation of (a) R$^\bullet$ and BNA$^+$ rather than (b) R$^+$ and BNA$^\bullet$ in Scheme 2. In the absence of O_2, t-Bu$^\bullet$ formed initially in the C-C bond cleavage of t-BuBNAH$^{\bullet+}$ will be further oxidized by $[\mathrm{Fe(phen)_3}]^{3+}$ to yield t-Bu$^+$ which then reacts with MeCN and/or residual water to yield t-BuNHCOMe or t-BuOH, or deprotonates to yield 2-methylpropene (Table 2), resulting in the 1:2 stoichiometry. In the presence of O_2, however, t-Bu$^\bullet$ will be trapped efficiently by O_2 to yield *tert*-butylperoxyl radical (t-BuOO$^\bullet$) which is not further oxidized by $[\mathrm{Fe(phen)_3}]^{3+}$ and it may be converted to the final product, t-BuOH by the radical reactions.[12] This is consistent with the 1:1 stoichiometry of t-BuBNAH to $[\mathrm{Fe(phen)_3}]^{3+}$ in the presence of O_2. When the large concentration of $[\mathrm{Fe(phen)_3}]^{3+}$ (1.0×10^{-2} or 2.5×10^{-2} mol dm^{-3}) is employed (Table 2) as compared to that in determination of the stoichiometry (1.0×10^{-4} mol dm^{-3}), the further oxidation of t-Bu$^\bullet$ by $[\mathrm{Fe(phen)_3}]^{3+}$ competes with the trap with O_2 leading to the formation of t-BuNHCOMe even in the presence of O_2 although the yield becomes smaller (Table 2).

The formation of t-BuOO$^\bullet$ ($g = 2.016$) upon the oxidation of t-BuBNAH (5.0×10^{-4} mol dm^{-3}) by $[\mathrm{Fe(phen)_3}]^{3+}$ (5.0×10^{-4} mol dm^{-3}) in aerated MeCN is confirmed by the ESR spectrum with a rapid mixing flow apparatus as shown in Figure 1. If the cleavage of the C(4)-C bond of t-BuBNAH$^{\bullet+}$ results in formation of t-BuBNA$^\bullet$ and H$^+$, electron transfer from t-BuBNA$^\bullet$ to O_2 in the presence of H$^+$ would occur to produce $\mathrm{HO_2}^\bullet$. However, no ESR spectrum other than t-BuOO$^\bullet$ has been observed in aerated MeCN. Thus, it can be concluded that RBNAH$^{\bullet+}$ formed in the electron transfer oxidation of RBNAH undergoes the C(4)-H or C(4)-C bond cleavage depending on the substituent R and that the cleavage of the C(4)-C bond of t-BuBNAH$^{\bullet+}$ results in formation of t-Bu$^\bullet$ and BNA$^+$ rather than t-Bu$^+$ and BNA$^\bullet$.

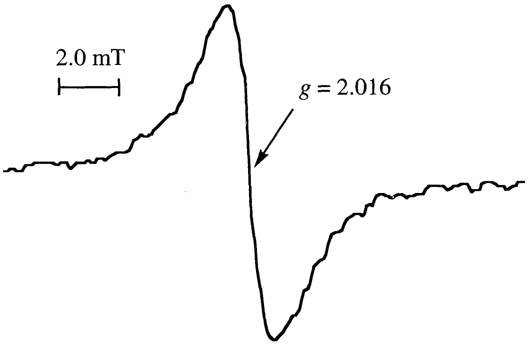


Figure 1. Transient ESR spectrum observed in the electron transfer oxidation of t-BuBNAH (5.0×10^{-4} mol dm^{-3}) by $[\mathrm{Fe(phen)_3}]^{3+}$ (5.0×10^{-4} mol dm^{-3}) in aerated MeCN.

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6 The one-electron oxidation potentials (*vs.* SCE) of t-Bu$^\bullet$ (0.09 V)[7] and BNA$^\bullet$ (-1.08 V)[3] are significantly lower than the one-electron oxidation potential of BNAH (0.57 V)[3].

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