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Mechanistic Investigations on the Reaction between Amines or Amides and an Alkylperoxy-λ^3-iodane

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Abstract: A mechanism involving the intermediate formation of an amine radical cation by single-electron transfer is proposed for the oxidation of secondary amines with alkylperoxy-λ^3-iodane. On the other hand, the oxidation of acetamides probably proceeds by a radical process, which involves the direct hydrogen abstraction of the methylene group α to the nitrogen atom.

Compound **1**[1] is a stable solid alkylperoxy-λ^3-iodane that can be safely stored at room temperature for an indefinite period of time. In contrast, it gradually decomposes in solution at room temperature to generate *tert*-butylperoxy radical **2** and *o*-iodobenzoyloxy radical **3** via homolytic bond cleavage of the hypervalent iodine(III)−peroxy bond (Figure 1). This property implies that alkylperoxy-λ^3-iodane **1** would be a very important reagent capable of performing the radical oxidation of a variety of organic compounds under mild conditions.[2] For example, we reported that the oxidation of secondary and tertiary amines with **1** proceeded at room temperature to yield imines and *tert*-butylperoxyamino acetals, respectively.[3] Alkylperoxy-λ^3-iodane **1** also oxidized the methylene groups α to the nitrogen atom of amides (or carbamates) yielding imides or *tert*-butylperoxyamido acetals.[4] We proposed that these reactions probably proceeded by a radical process. We report here mechanistic investigations on the reactions of amines or amides with alkylperoxy-λ^3-iodane **1** by measuring the relative rates of oxidation and the kinetic deuterium isotope effects.

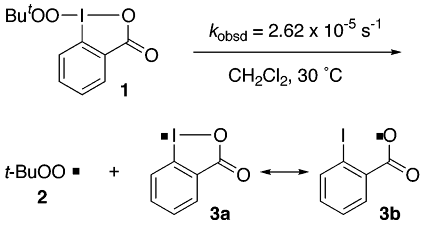
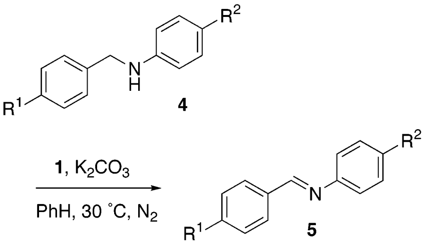


FIGURE 1. Homolytic cleavage of the hypervalent iodine(III)−peroxy oxygen bond.

SCHEME 1. Competitive Reactions of Oxidation for *N*-Benzylaniline Derivatives 4 with 1



4, 5a: R^1 = R^2 = H
4, 5b: R^1 = OMe, R^2 = H
4, 5c: R^1 = Me, R^2 = H
4, 5d: R^1 = Cl, R^2 = H
4, 5e: R^1 = H, R^2 = OMe
4, 5f: R^1 = H, R^2 = Me
4, 5g: R^1 = H, R^2 = Cl

TABLE 1. Relative Reactivity of *N*-Benzylanilines 4a−d with 1 at 30 °C

substrate	k_{rel}[a]
4b (R^1 = OMe)	1.07
4c (R^1 = Me)	0.88
4a (R^1 = H)	1.00
4d (R^1 = Cl)	1.13

[a] Relative rates were determined by ^{1}H NMR.

Our initial studies focused on the substituent effect on the phenyl ring in the benzylic group or the aniline moiety of *N*-benzylaniline (Scheme 1). The relative rates of oxidation for the *p*-substituent R^1 in the benzylic group of *N*-benzylaniline were measured at 30 °C in benzene by competitive reactions, in which a mixture of 25-fold excesses of two competing substrates was used. No significant substituent effect was observed for the *p*-substituent R^1 on the phenyl ring in the benzylic group of *N*-benzylaniline. Furthermore, the Hammett correlation plot for the oxidation of these *N*-benzylanilines **4a**−**d** presented in Table 1 did not show a good correlation. This result indicates that the rate-determing step of the reactions does not involve C−H bond cleavage of the benzylic methylene group, which surprised us greatly, since we reported that the rate-determing step of the oxidation of benzyl ethers with **1**[2d] probably involves a high degree of benzylic C−H bond breaking.

We also examined whether the *p*-substituent R^2 on the phenyl ring in the aniline moiety of *N*-benzylaniline (**4a**,**e**−**g**) influences the reaction rate under similar reaction conditions described above. The results are shown in Table 2, and it is observed that the reactivity of *N*-benzylaniline **4** depends strongly on the nature of substituent R^2. Electron-releasing groups such as MeO (**4e**) and Me (**4f**) increase the rate of oxidation, and an electron-withdrawing group such as Cl (**4g**) decreases the rate of oxidation, suggesting that the electronic state in the aniline moiety is very important for the oxidation of *N*-benzylaniline with **1**.

The plot of the relative reactivity of **4a** or **4e**−**g** vs the σ^+ value gave a linear correlation with a value of $\rho^+ =$

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[1] Synthesis and characterization of alkylperoxy-λ^3-iodane **1**, see: Ochiai, M.; Ito, T.; Masaki, Y.; Shiro, M. *J. Am. Chem. Soc.* **1992**, *114*, 6269. Alkylperoxy-λ^3-iodane **1** can now be purchased from Tokyo Kasei Kogyo Co., Ltd.

[2] For our studies of oxidation reactions with alkylperoxy-λ^3-iodane **1**, see the following. (a) Oxidative ring cleavage of cyclic acetals: Sueda, T.; Fukuda, S.; Ochiai, M. *Org. Lett.* **2001**, *3*, 2387. (b) Oxidation of para-substituted phenols: Ochiai, M.; Nakanishi, A.; Yamada, A. *Tetrahedron Lett.* **1997**, *38*, 3927. (c) Oxidation of sulfides: Ochiai, M.; Nakanishi, A.; Ito, T. *J. Org. Chem.* **1997**, *62*, 4253. (d) Oxidation and deprotection of benzyl and allyl ethers: Ochiai, M.; Ito, T.; Takahashi, H.; Nakanishi, A.; Toyonari, M.; Sueda, T.; Goto, S.; Shiro, M. *J. Am. Chem. Soc.* **1996**, *118*, 7716.

[3] Ochiai, M.; Kajishima, D.; Sueda, T. *Heterocycles* **1997**, *46*, 71.

[4] Ochiai, M.; Kajishima, D.; Sueda, T. *Tetrahedron Lett.* **1999**, *40*, 5541.

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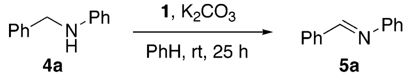
TABLE 2. Relative Reactivity of *N*-Benzylanilines 4a and 4e−g with 1 at 30 °C

substrate	k_{rel}[a]	σ^{+b}	IP[c] (eV)
4e	12.80	−0.78	8.27
4f	4.43	−0.31	8.40
4a	1.00	0	8.52
4g	1.02	0.11	8.51

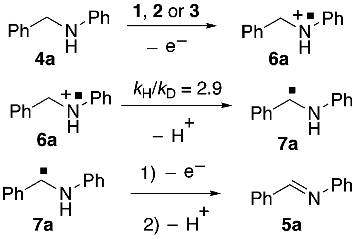
[a] Relative rates were determined by ^{1}H NMR. [b] See ref 5. [c] IP = ionization potential. See ref 6.

SCHEME 2. Reaction of *N*-Benzylaniline 4a with 1 in the Presence of TEMPO



additive	yield (%)
-	84
TEMPO	100

SCHEME 3. Mechanism for Reaction of *N*-Benzylaniline 4a with Alkylperoxy-λ^3-iodane 1



−1.32 (r = 0.98). This ρ^+ value appears to be comparable to $\rho^+ = -1.8$ or −1.1 for an electron transfer from the aniline moiety in *N*-benzylaniline by a cobalt Shiff base complex.[7] Moreover, good correlation of the relative reactivity with the ionization potential (IP) of **4a** or **4e**−**g** was also observed. These results suggest that the rate-determining step for oxidation of *N*-benzylanilines **4** with **1** most probably involves an electron transfer from **4** to give anilinium radical cations **6a** (Scheme 3).

Since it is not clear whether single-electron transfer occurs from *N*-benzylaniline **4a** to alkylperoxy-λ^3-iodane **1** or to *tert*-butylperoxy radical **2** or *o*-iodobenzoyloxy radical **3** generated from decomposition of **1**, next we examined the effect of free-radical scavengers. If the electron transfer from amine to radical species **2** or **3** is a major process, the oxidation may be prevented by the free-radical scavenger. However, the reaction of *N*-benzylaniline **4a** with **1** in the presence of 2,2,6,6-tetramethylpiperidinyloxy free-radical (TEMPO) under an argon atmosphere gave *N*-benzylideneaniline **5a** in high yield (Scheme 2).

TEMPO has recently been reported to promote reactions involving hypervalent organoiodane reagents.[8a] For example, Margarita and Piancatelli reported that alcohols were oxidized to the corresponding aldehydes and ketones in good yield when a catalytic amount of TEMPO was used in combination with (diacetoxy)iodobenzene as stoichiometric oxidants. In these reactions, 2,2,6,6-tetramethylpiperidinium salt[9] generated in situ oxidizes alcohols to aldehydes or ketones.[8b] Furthermore, it is known that *N*-oxoammonium salts can oxidize tertiary amines to give the corresponding immonium salts.[10] Therefore, under our conditions, an *N*-oxoammonium salt is possibly generated from the reaction of TEMPO with **1** and oxidizes *N*-benzylaniline **4a** to *N*-benzylideneaniline **5a**.[11] Attempts to further study the effects of a radical scavenger by addition of a galvinoxyl free-radical also were unsuccessful.[12]

We also compared the electron affinities (EA) of alkylperoxy-λ^3-iodane **1**, *tert*-butylperoxy radical **2**, and *o*-iodobenzoyloxy radical **3b** by using a computational analysis. Brinck estimated the EA of **2** to be −1.20 eV,[13] and this is in agreement with experimental data (−1.20 eV).[14] We also estimate the EA of **1** and **3b** to be +0.686 and −2.54 eV, respectively, by using the Gaussian 98 program.[15] Compared to those, *o*-iodobenzoyloxy radical **3b** is the most electron-accepting and single-electron transfer is not likely to occur from *N*-benzylaniline **4a** to **1**. This hypothesis should be discussed when the cleavage of the hypervalent iodine(III)−peroxy bond of the alkylperoxy-λ^3-iodane **1** proceeds smoothly. Therefore, we estimated homolytic bond dissociation enthalpy (BDE) for the hypervalent iodine(III)−peroxy bond of the alkylperoxy-λ^3-iodane **1** to be 1.84 eV.[16] Since the BDE is

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(5) Brown, H. C.; Okamoto, Y. *J. Am. Chem. Soc.* **1958**, *80*, 4979.

(6) PM3 calculations were carried out using the MOPAC 97 series of programs. A variety of conformations, generated by internal rotation about single bonds, were considered, and subsequent IP calculations were performed on the lowest energy forms.

(7) (a) Maruyama, K.; Kusukawa, T.; Higuchi, Y.; Nishinaga, A. *Chem. Lett.* **1991**, 1991. (b) Nishinaga, A.; Yamazaki, S.; Matsuura, T. *Tetrahedron Lett.* **1988**, *29*, 4115.

(8) (a) de Mico, A.; Margarita, R.; Mariani, A.; Piancatelli, G. *Tetrahedron Lett.* **1996**, *37*, 1889. (b) de Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974.

(9) *N*-Oxoammonium salts have been demonstrated to be useful reagents for the transformation of alcohols; see: de Nooy, A. E. J.; Besemer, A. C.; VanBekkum, H. *Synthesis* **1996**, 1153.

(10) (a) Bobbitt, J. M.; Ma, Z. *Heterocycles* **1992**, *33*, 641. (b) Hunter, D. H.; Barton, D. H. R.; Motherwell, W. J. *Tetrahedron Lett.* **1984**, *25*, 603.

(11) We calculated the ionization potentials of TEMPO and *N*-benzylaniline **4a** at the B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d) level of theory to give very similar values of 6.99 and 7.00 eV, respectively.

(12) Galvinoxyl reacts with *tert*-amines via single-electron transfer to give ammonium radical cations; see: Screttas, C. G.; Heropoulos, G. A. *Magn. Res. Chem.* **1990**, *28*, 878.

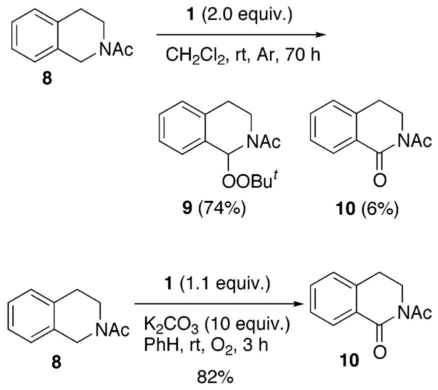
(13) Brinck, T.; Lee, H.-N.; Jonsson, M. *J. Phys. Chem. A* **1999**, *103*, 7094.

(14) Clifford, E. P.; Wenthold, P. G.; Garejev, R.; Lineberger, W. C.; Depuy, C. H.; Bierbaum, V. M.; Ellison, G. B. *J. Chem. Phys.* **1998**, *109*, 10293.

(15) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.11; Gaussian, Inc.: Pittsburgh, PA, 1998. Optimized and harmonic frequencies for alkylperoxy-λ^3-iodane **1**, the radical anion of (alkylperoxy)iodane, *o*-iodobenzoyloxy radical **3b**, and *o*-iodobenzoyloxy anion have been computed at the UHF/3-21G level of theory. We have also performed single-point energy calculations for the molecules at the UB3LYP/3-21G* level using UHF/3-21G geometries. The EA energy expression in UB3LYP/3-21G* has the following form: EA (**1**) = E(radical anion of **1**) − E(**1**); EA (**3b**) = E(*o*-iodobenzoyloxy anion) − E(**3b**).

(16) Optimized and harmonic frequencies for *tert*-butylperoxy radical **2** have been computed at the UB3LYP/6-31G(d) level of theory, and we have performed single-point energy calculations for **2** at the UB3LYP/3-21G* level using UB3LYP/6-31G(d) geometries. The BDE energy expression in UB3LYP/3-21G* has the following form: BDE (**1**) = [E(**2**) + E(**3b**)] − E(**1**)

SCHEME 4. Oxidation of *N*-Acetyl-1,2,3,4-tetrahydroisoquinoline 8 with 1



extremely high as compared with EA of **1** or *tert*-butylperoxy radical **2** or *o*-iodobenzoyloxy radical **3b**, it is very difficult to determine which species accepts an electron from secondary amines.

A reaction mechanism for *N*-benzylaniline **4a** with alkylperoxy-λ^3-iodane **1** is illustrated in Scheme 3.

Electron loss from **4a** gives anilinium radical cation **6a**, which undergoes deprotonation promoted by *tert*-butylperoxy anion or *o*-iodobenzoyloxy anion to give an α-amino carbon radical **7a**. The hydrogen/deuterium isotope effect for *N*-benzylaniline **4a** labeled at the methylene group α to nitrogen was measured, and a small deuterium kinetic isotope effect $k_H/k_D = 2.9$ was obtained. This value is slightly bigger than $k_H/k_D = 1.3$ previously observed for an electron transfer from the aniline moiety by a cobalt Shiff base.[7a] This difference is now not clear, but it should be noted that comparison of isotope effects for the deprotonation of amine cation radicals is very complicated and the isotope effects need not to be small.[17] The α-amino carbon radical **7a**, a very easily oxidizable species,[18] is oxidized to a carbocation, which is then converted into an imine **5a** by deprotonation from nitrogen.

Alkylperoxy-λ^3-iodane **1** also oxidizes the methylene group α to the nitrogen atom of amides (or carbamates) yielding imides or *tert*-butylperoxyamido acetals.[3] This reaction is sensitive to the reaction conditions. When the reaction was carried out in argon, the peroxyamido acetals were produced as a major product, while in oxygen, the major product was imides. In this case, oxidation of *N*-acetyl-1,2,3,4-tetrahydroisoquinoline **8** in the presence of a catalytic amount of **1** yielded 2-acetyl-3,4-dihydro-2*H*-isoquinolin-1-one **10** in high yield (Scheme 4).

The variations in the product profiles are in good agreement with the alkylperoxy-λ^3-iodane **1** oxidation of benzyl ethers, involving intermediacy of the α-oxy benzylic radicals generated from benzylic hydrogen abstraction of benzyl ethers with iodanyl radical **3a** or benzoyloxy radical **3b**.[2d] Accordingly, oxidation of amides with **1** also may involve hydrogen abstraction of the methylene group α to the nitrogen atom, generating α-amido carbon radicals. Actually, we have reported that the radical nature of the oxidation was substantiated by the inhibition of the reaction with an added radical scavenger, a galvinoxyl free-radical, in a previous paper.[3]

SCHEME 5. Competitive Reactions of Oxidation for *N*-Benzylacetamides 10a−e with 1

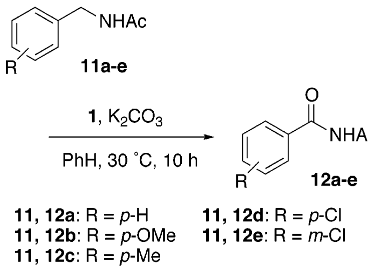


TABLE 3. Oxidation of *N*-Benzylacetamides 11 with Alkylperoxy-λ^3-iodane 1[a]

			products (yields[b], %)	
entry	**11**	time	**12**	**11** (recovered)
1	**11a**	26 h	**12a** (52)	**11a** (42)
2	**11b**	48 h	**12b** (65)	**11b** (21)
3	**11c**	48 h	**12c** (45)	**11c** (29)
4	**11d**	48 h	**12d** (37)	**11d** (49[c])
5	**11e**	48 h	**12e** (34)	**11e** (48)

[a] Reactions were carried out using 2 equiv of **1a** and 10 equiv of K_2CO_3 at room temperature in benzene under O_2. [b] Isolated yields. [c] NMR yield.

TABLE 4. Relative Reactivity of *N*-Benzylacetamides 11 with 1 at 30 °C

substrate	k_{rel}[a]	σ	σ^{+} [b]	IP[c] (eV)
11b (*p*-OMe)	1.62	−0.268	−0.778	9.19
11c (*p*-Me)	1.38	−0.17	−0.311	9.47
11a (H)	1	0	0	9.60
11d (*p*-Cl)	0.843	0.227	0.114	9.43
11e (*m*-Cl)	0.690	0.37	0.40	9.47

[a] Relative rates were determined by ^{1}H NMR. [b] See ref 5. [c] IP = ionization potential. See ref 6.

To gain further detailed insight into the mechanism of the oxidation of amides by **1**, the relative rates of oxidation for the substituent R in the benzylic group of *N*-benzylacetamides **11** were measured at 30 °C in benzene by competitive reactions under molecular oxygen, in which a mixture of 25-fold excesses of two competing substrates was used (Scheme 5). Table 3 shows that the reactions of *N*-benzylacetamides **11a**−**e** with **1** are very slow, and even after 48 h, a large amount of the starting amides was recovered.

The effect of substituents on the rate of oxidation is also shown in Table 4. Electron-releasing groups such as *p*-MeO and *p*-Me increase the rate of oxidation. Hammett correlation plots for the oxidation of these acetamides **11a**−**e** showed a good correlation of relative rate factors with the σ and σ^+ constants of substituents in the aromatic ring and afforded the reaction constants $\rho = -0.56$ ($r = 0.99$) and $\rho^+ = -0.33$ ($r = 0.97$). These negative small ρ and ρ^+ values appear to be comparable to $\rho^+ = -0.30$ for benzylic hydrogen abstractions from benzyl butyl ethers by an iodanyl radical or a benzoyloxy

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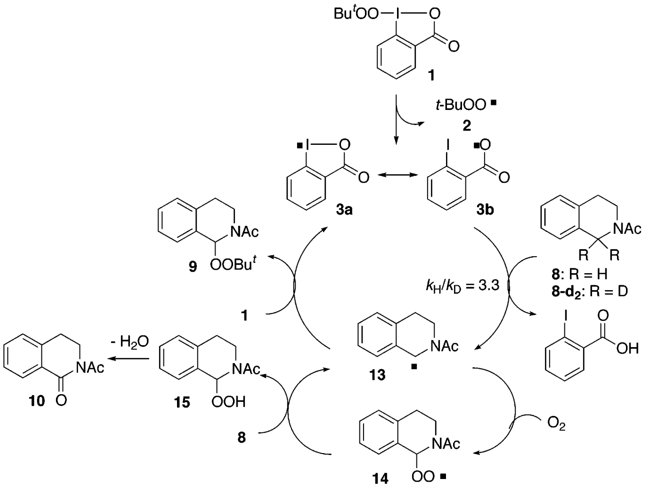
(17) (a) Karki, S. B.; Dinnocenzo, J. P.; Jones, J. P.; Korzekwa, K. R. *J. Am. Chem. Soc.* **1995**, *117*, 3657. (b) Dinnocenzo, J. P.; Karki, S. B.; Jones, J. P. *J. Am. Chem. Soc.* **1993**, *115*, 7111.

(18) (a) Baciocchi, E.; Gerini, M. F.; Lanzalunga, O.; Lapi, A.; Mancinelli, S.; Mencarelli, P. *Chem. Commun.* **2000**, 393. (b) We calculated the ionization potential of anilinium radical cation **6a** at the B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d) level of theory as 5.62 eV.

SCHEME 6. Mechanism for Oxidation of *N*-Acetyl-1,2,3,4-tetrahydroisoquinoline 8 with Alkylperoxy-λ^3-iodane 1



radical generated from bond cleavage of the hypervalent iodine(III)−peroxy bond of alkylperoxy-λ^3-iodane **1**.[2d]

As illustrated in Scheme 6, a reaction mechanism for the oxidation of amides with **1** probably involves the following key steps: (a) homolytic bond cleavage of the hypervalent iodine(III)−peroxy bond of **1** generating *tert*-butylperoxy radical **2** and iodanyl radicals **3a**,**b**, (b) hydrogen abstraction of the methylene group α to the nitrogen atom by iodanyl radical **3a** or benzoyloxy radical **3b**,[19] or (c) nucleophilic attack of the α-amido carbon radical **13** to the iodine(III)−peroxy bond of (alkylperoxy)-iodane **1** yielding the *tert*-butylperoxyamido acetal **9**. Hydrogen abstraction of the methylene group α most likely involves a rate-limiting step from the deuterium kinetic isotope effect $k_H/k_D = 3.3$ measured for the oxidation of protonated and deuterated *N*-acetyl-1,2,3,4-tetrahydroisoquinolines **8**-d_2 in dichloromethane at 30 °C under argon. Similarly, Hall and Hanzlik reported that intramolecular kinetic deuterium isotope effects measured for the enzymic N-demethylation of aromatic and aliphatic *N*-methyl-*N*-trideuteriomethyl amides, RCON-$(CH_3)CD_3$, varied from 3.6 to 6.9, and this suggests that the mechanism involves hydrogen atom abstraction.[20] In the presence of oxygen, the following alternative pathway would be preferred: (a) reactions of α-amido carbon radicals **13** with oxygen generating peroxy radical **14** and (b) hydrogen abstraction with the peroxy radical **14** yielding the hydroperoxy amido acetal **15** with concomitant α-amido carbon radicals **13** and decomposition of the hydroperoxy amido acetal **15** to produce imide **10**. Note that the decomposition of the *tert*-butylperoxy amido acetal **9** to produce imide **10** does not occur under the reaction conditions (Table 5).

TABLE 5. Reactivity of *tert*-Butylperoxyamido Acetal 9[a]

entry	1	K_2CO_3	**10**	**9** (recovered)
1			0	99
2	1.2		0	76
3		10	0	97
4	1.2	10	0	83

[a] Reactions were carried out at room temperature in PhH under O_2 for 3 h.

An alternative pathway to the formation of the α-amido carbon radicals **13** involves electron transfer, which generates amide cation radicals, and subsequent proton transfer. But this reaction process seems not to proceed since the oxidation of acetamides **11a**−**e** showed no correlation of the relative rate factors with the corresponding calculated ionization potential of amides. Furthermore, deuterium kinetic isotope effects are significantly larger than those observed for the electron-transfer mechanism[22] and are consistent with a mechanism involving hydrogen atom abstraction.

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Supporting Information Available: Text describing experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Abstraction of benzylic α-hydrogen by an iodanyl radical or an *o*-iodobenzoyloxy radical was discussed in ref 2d and references therein in detail.

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(21) (a) Murata, S.; Miura, M.; Nomura, M. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1259. (b) Shono, T.; Hamaguchi, H.; Matsumura, Y. *J. Am. Chem. Soc.* **1975**, *97*, 4264.

(22) Davis, R. V.; Brian, I. B.; Suschitzky, H.; Gittos, M. W. *J. Chem. Soc., Perkin Trans. 1* **1978**, 180.