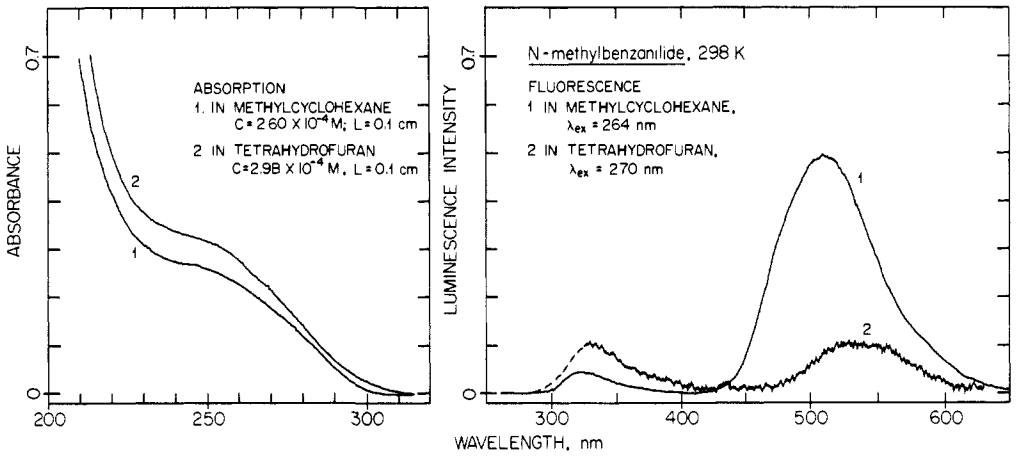

Figure 1. Spectra of *N*-methylbenzanilide in solution at 298 K.

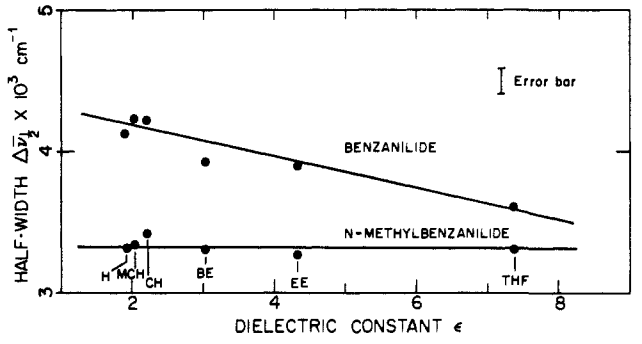

Figure 2. Spectroscopic half-width (FWHM) of 500-nm region fluorescence bands of benzanilides at 298 K. Solvents H (hexane), MCH (methylcyclohexane), CH (cyclohexane), BE (dibutyl ether), EE (diethyl ether), THF (tetrahydrofuran).

The fluorescence spectra of benzanilide compared with those of *N*-methylbenzanilide, however, reveal an additional complexity in the former. First of all, the half-width of the green fluorescence of benzanilide (onset 400 nm, λ_{max} 475 nm, MCH at 298 K) proves to be substantially greater than that of *N*-methylbenzanilide, $\Delta\bar{\nu}$ = 4115 cm^{-1} vs 3316 cm^{-1}. Secondly, the benzanilide fluorescence half-width markedly contracts as the dielectric constant increases from 1.92 (H) to 7.39 (THF), whereas, the *N*-methylbenzanilide fluorescence half-width remains constant. Figure 2 gives a plot of fluorescence band half-width (FWHM) versus dielectric constant for various solvents; a parallel behavior is observed for the E_T index.[5] These and related observations[6] suggest that *in benzanilide the observed blue-green fluorescence band consists of two independent overlapping fluorescence in hydrocarbon solution at 298 K.* Thus, the report by Tang, MacInnis, and Kasha[2] interpreting the long wavelength fluorescence as being of proton-transfer tautomer origin is supported in part. Recently Tang confirmed the presence of H-bonding dimer formation in benzanilide by infrared spectral studies,[7] adding confidence to the H-bonded dimer proton-transfer mechanism proposed earlier.[2]

The photochemical study of benzanilide and related molecules[8-10] and the striking rearrangements observed require a detailed understanding of the electronic excited states giving rise to the photochemical products. The initial fluorescence anomaly reported by O'Connell et al.[1] has proved to be unusually subtle. The present study has been extended in several directions, most particularly to picosecond dynamics. These latter results confirm three modes of depopulating the initially excited singlet state, as evidenced by the steady-state spectroscopy studies presented here. A comprehensive paper on these and related results is in preparation.

Acknowledgment. Work done under Contract No. DE-FG05-87ER60517 between the Division of Biomedical and Environmental Research, U.S. Department of Energy, and the Florida State University. The assistance of Dr. Janusz Rachon in this research is gratefully acknowledged, for his part in the synthesis of *N*-methylbenzanilide and for stimulating discussions of the charge-transfer interpretation.

Registry No. I, 1934-92-5; benzanilide, 93-98-1.

(6) Heldt, J.; Gormin, D.; Kasha, M. *Chem. Phys. Lett.*, in Press.
(7) Tang, G.-Q., private communication, to be published.
(8) Carlsson, D. J.; Gan, L. H.; Wiles, D. M. *Can. J. Chem.* **1975**, *53*, 2337-2344.
(9) Schwetlick, T.; Stumpe, J.; Noack, R. *Tetrahedron* **1979**, *35*, 63-68.
(10) Chênevert, R.; Plante, R. *Can. J. Chem.* **1983**, *61*, 1092-1095.

Ruthenium-Catalyzed Cytochrome P-450 Type Oxidation of Tertiary Amines with Alkyl Hydroperoxides

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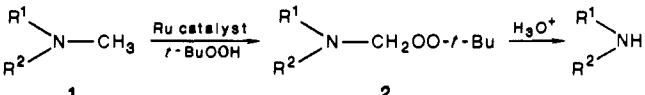
Oxidative N-dealkylation of amines is one of the important P-450 specific reactions,[1] and several model reactions using iron porphyrins have been reported.[2,3] During the course of our systematic studies on the simulation of enzymatic function of metabolism of amines with transition-metal catalysts,[4] we have found novel cytochrome P-450 type oxidation behavior with tertiary amines.

The ruthenium-catalyzed reaction of tertiary amines **1** with *tert*-butyl hydroperoxide gives the corresponding α-(*tert*-butyldioxy)alkylamines **2** highly efficiently (eq 1).[5] The reaction



(1)

(1) (a) *Cytochrome P-450*; Sato, R., Omura, T., Eds.; Kodansha Ltd: Tokyo, 1978. (b) Gorrod, J. W. *Biological Oxidation of Nitrogen*; Elsevier/North Holland Biomedical Press: New York, 1978.
(2) (a) Shannon, P.; Bruice, T. C. *J. Am. Chem. Soc.* **1981**, *103*, 4580. (b) Dicken, C. M.; Lu, F.-L.; Nee, M. W.; Bruice, T. C. *Ibid.* **1985**, *107*, 5776. (c) Ostovic, D.; Knobler, C. B.; Bruice, T. C. *Ibid.* **1987**, *109*, 3444.
(3) (a) Santa, T.; Miyata, N.; Hirobe, M. *Chem. Pharm. Bull.* **1984**, *32*, 1252. (b) Fujimori, K.; Fujiwara, S.; Takata, T.; Oae, S. *Tetrahedron Lett.* **1986**, *27*, 581. (c) Lindsay Smith, J. R.; Mortimer, D. N. *J. Chem. Soc., Chem. Commun.* **1985**, 64.
(4) (a) Murahashi, S.-I.; Hirano, T.; Yano, T. *J. Am. Chem. Soc.* **1978**, *100*, 348. (b) Murahashi, S.-I.; Watanabe, T. *Ibid.* **1979**, *101*, 7429. (c) Murahashi, S.-I.; Yoshimura, N.; Tsumiyama, T.; Kojima, T. *Ibid.* **1983**, *105*, 5002. (d) Mitsui, H.; Zenki, S.; Shiota, T.; Murahashi, S.-I. *J. Chem. Soc., Chem. Commun.* **1984**, 874. (e) Murahashi, S.-I.; Naota, T.; Taki, H. *J. Chem. Soc., Chem. Commun.* **1985**, 613.

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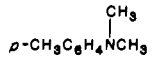
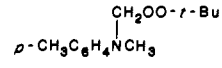
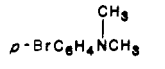
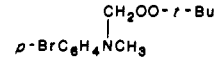
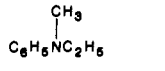
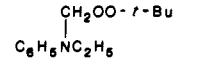
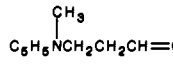
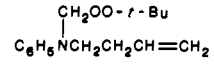
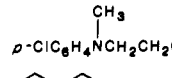
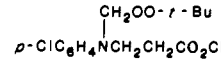
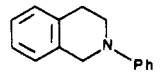
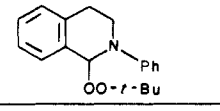
Table I. Ruthenium-Catalyzed Reaction of Tertiary Amines with *t*-BuOOH[a]

entry	tertiary amine	*t*-BuOOH (equiv)	product[b]	yield[c] (%)
1		2.2		93 (97)[d]
2		2.2		96
3		2.2		83 (97)[d]
4		3.5		78
5		3.5		87
6		3.0		80
7		3.0		65

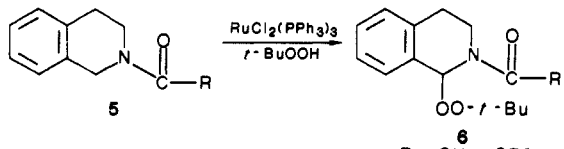
[a] The procedure is described in the text. [b] Satisfactory IR and NMR spectral data were obtained. [c] Isolated yield. [d] *t*-BuOOH (2.5 equiv) in toluene was used.

provides a new strategy for the generation of iminium ion intermediates from **2** upon treatment with acids, and hence selective N-demethylation of tertiary *N*-methylamines and construction of piperidine skeletons from *N*-methylhomoallylamines via olefin–iminium ion cyclizations can be performed efficiently.

The catalytic activity of various metal complexes was examined for the oxidation of *N,N*-dimethylaniline (**3**) with *tert*-butyl hydroperoxide. $RuCl_2(PPh_3)_3$ has proven to be the most effective catalyst for the formation of *N*-methyl-*N*-(*tert*-butyldioxymethyl)aniline (**4**).[6] As shown in Table I tertiary methylamines can be converted into the corresponding *tert*-butyldioxymethylamines efficiently. In a typical case, to a mixture of **3** (0.242 g, 2.00 mmol) and $RuCl_2(PPh_3)_3$ (0.058 g, 0.06 mmol) in benzene (3.0 mL) was added a 1.13 M solution of *t*-BuOOH in dry benzene (4.4 mmol, 3.9 mL) dropwise at room temperature over a period of 3 h under argon. The mixture was washed with water to remove excess *t*-BuOOH. Evaporation of the organic extract and short column chromatography on Florisil gave **4** (0.389 g, 93%).

Usually, the transition-metal-catalyzed oxidation of tertiary amines with hydroperoxides gives the corresponding amine *N*-oxides;[7] however, such products are not obtained in the present reaction. Substituted *N,N*-dimethylanilines were converted into the corresponding *tert*-butyldioxyamines regardless of the substituents on the aryl group. Benzylic and allylic positions and carbon–carbon double bonds tolerate the oxidation. *N*-Methyl groups are oxidized chemoselectively in the presence of other alkyl and alkenyl groups. The *tert*-butyldioxy group is introduced at the C-1 position of 1,2,3,4-tetrahydroisoquinolines.

Importantly, amides are also oxidized readily at the α-positions of nitrogen. Thus, the ruthenium-catalyzed reaction of *N*-acyl-1,2,3,4-tetrahydroisoquinolines, **5a** and **5b**, with *t*-BuOOH gave **6a** and **6b** in 87% and 77% yields, respectively.



5 → **6**

a, R = CH_3 87%
b, R = Ph 77%

(5) The stoichiometry of this reaction has been determined. Oxidation of **1** with 2 equiv of *t*-BuOOH gives **2**, *t*-BuOH, and H_2O.

(6) The corresponding *N*-oxides were obtained by using the other catalysts such as $RhCl(PPh_3)_3$, $VO(acac)_2$, $Mo(CO)_6$, $MoO_2(acac)_2$, and SeO_2.

(7) Sheldon, R. A.; Kochi, J. K. *Metal-Catalyzed Oxidations of Organic Compounds*; Academic Press: New York, 1981; p 387.

Table II. Selective N-Demethylation of Tertiary Methylamines[a]

entry	tertiary amine	product	yield[b] (%)
1	$C_6H_5N(CH_3)_2$	$C_6H_5NHCH_3$	83
2	p-$CH_3OC_6H_4N(CH_3)_2$	p-$CH_3OC_6H_4NHCH_3$	87 (81)[c]
3	p-$BrC_6H_4N(CH_3)_2$	p-$BrC_6H_4NHCH_3$	84
4	$C_6H_5N(CH_3)(C_2H_5)$	$C_6H_5NHC_2H_5$	61
5	$C_6H_5N(CH_3)(C_4H_9)$	$C_6H_5NHC_4H_9$	66

[a] Peroxide **2** which was prepared according to the procedure described in the text was treated with a 2 N HCl solution in ether at room temperature. [b] Isolated yield based on the starting tertiary amines. [c] Cumyl hydroperoxide (3.0 equiv) was used in place of *t*-BuOOH.

In order to gain insight into the mechanism the relative reaction rates of the oxidation of five substituted *N,N*-dimethylanilines (X-$C_6H_4N(CH_3)_2$, X = *p*-CH_3O, *p*-CH_3, H, *p*-Cl, and *m*-Cl) with *t*-BuOOH in benzene were determined by the ^1H NMR analysis of the product peroxides.[3c] The rate data correlate well (γ = 0.974) with the Hammett linear free energy relationship with use of σ values. The ρ value is −0.84, which indicates cationic intermediacy at the rate-determining step. The intramolecular deuterium isotope effect of the ruthenium-catalyzed oxidation of *N*-methyl-*N*-(trideuteriomethyl)aniline was determined to be 3.53 by means of the NMR analyses of the product peroxides. Furthermore, the intermolecular isotope effect[10a] of the oxidation of *N,N*-dimethylanilines was determined to be 1.64 by the NMR analysis of the demethylated products of the competitive reaction of *N,N*-dimethylaniline and *N,N*-bis(trideuteriomethyl)aniline. The observed intra- and intermolecular isotope effects (3.53 and 1.64) are larger than the values observed for P-450 N-demethylations (1.6–3.1[8] and 1.0–1.1[9,10a]), suggesting that the C–H bond breaking in the present reaction proceeds with more radical character. Although it is premature to discuss the precise mechanism at the present stage, the reaction can be rationalized by assuming the P-450 type mechanism.[10] A ruthenium(II) complex reacts with hydroperoxide to give an oxoruthenium(IV) species.[11] The reaction of the Ru(II) complex with *t*-BuOOH

(8) (a) Shono, T.; Toda, T.; Oshino, N. *J. Am. Chem. Soc.* **1982**, *104*, 2639. (b) Miwa, G. T.; Garland, W. A.; Hodshon, B. J.; Lu, A. Y. H.; Northrop, D. B. *J. Biol. Chem.* **1980**, *255*, 6049. (c) Miwa, G. T.; Walsh, J. S.; Kedderis, G. L.; Hollenberg, P. F. *Ibid.* **1983**, *258*, 14445.

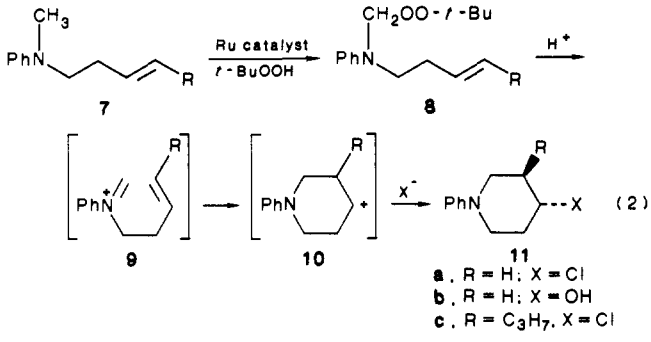
(9) (a) Thompson, J. A.; Holtzman, J. L. *Drug Metab. Dispos.* **1974**, *2*, 577. (b) Reference 8b.

(10) (a) Heimbrook, D. C.; Murray, R. I.; Egeberg, K. D.; Sligar, S. G.; Nee, M. W.; Bruice, T. C. *J. Am. Chem. Soc.* **1984**, *106*, 1514. (b) Burka, L. T.; Guengerich, F. P.; Willard, R. J.; Macdonald, T. L. *Ibid.* **1985**, *107*, 2549.

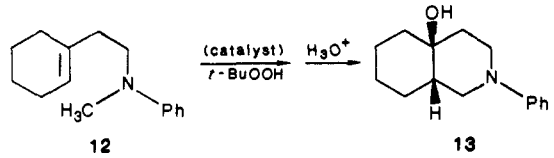
would give Ru(II)OOBu-*t*, which undergoes cleavage of the O–O bond to give Ru(IV)=O.[12] Tertiary amines would undergo oxidation with Ru(IV)=O species to give **2** similar to the formation of $R^1R^2NCH_2OH$ in the P-450 induced demethylation reactions.[10]

Selective N-demethylation of tertiary methylamines is performed by the present ruthenium-catalyzed oxidation and subsequent hydrolysis with an aqueous HCl solution (eq 1). This is the first synthetically practical method for the N-demethylation of tertiary methylamines although few catalytic[2,3] and stoichiometric reactions[13] have been reported. The representative results of the N-demethylation are listed in Table II. Methyl groups are removed chemoselectively in the presence of various alkyl groups.

The present reaction provides a novel, biomimetic method[14] for the construction of piperidine skeletons from *N*-methylhomoallylamine **7** via olefin–iminium ion cyclization reactions (eq 2).



The reported olefin–iminium ion cyclizations are limited to the reactions of the iminium ions which are derived from the condensation of primary or secondary amines with carbonyl compounds,[15] the reaction of imines with acetyl chloride,[16] and the protonolysis of reduced cyclic imides.[17] The ruthenium-catalyzed oxidation of *N*-methyl-*N*-(3-butenyl)aniline (**7a**) gave the peroxide **8a** (87%), which was converted to 1-phenyl-4-chloropiperidine (**11a**) (77%) upon treatment with a 2 N HCl solution at room temperature. Similar treatment of **7a** with a 0.4 N aqueous CF_3CO_2H solution gave 1-phenyl-4-hydroxypiperidine (**11b**) (50%). Cyclization of the peroxides **8** bearing a substituted 3-butenyl group gave *trans*-3,4-disubstituted piperidines stereoselectively. Thus, *trans*-1-phenyl-3-propyl-4-chloropiperidine (**11c**) has been obtained stereoselectively from *N*-methyl-*N*-(3-heptenyl)aniline (**7c**) (oxidation 76%; cyclization 55%). The reaction of cyclic amines gives only cis fused bicyclic amines. Thus, *cis*-4a-hydroxy-2-phenyldecahydroisoquinoline (**13**) was obtained from



N-methyl-*N*-2-(1-cyclohexenyl)ethylaniline (**12**) (85%; 44%) selectively upon treatment of the corresponding peroxide with an aqueous CF_3CO_2H solution. These cyclizations can be rationalized by assuming the formation of iminium ion **9** by protonation of **8** and subsequent elimination of *t*-BuOOH. Nucleophilic attack of an alkene gives carbonium ion **10**, which is trapped by nucleophile X^- from the less hindered side. It is noteworthy that recovered *t*-BuOOH can be used again.

Work is in progress to provide definitive mechanistic information and to apply our method to other systems.

Supplementary Material Available: Spectral data of the product peroxides, **11** and **13** (4 pages). Ordering information is given on any current masthead page.

(11) (a) Marmion, L. E.; Takeuchi, K. J. *J. Am. Chem. Soc.* **1986**, *108*, 510. (b) Roecker, L.; Meyer, T. J. *Ibid.* **1987**, *109*, 746.
(12) Groves, J. T.; Watanabe, Y. *J. Am. Chem. Soc.* **1986**, *108*, 7834.
(13) N-Dealkylation with a stoichiometric amount of oxidants is nonselective: Rosenblatt, D. H.; Burrows, E. P. In *The Chemistry of Amino, Nitroso and Nitro Compounds and Their Derivatives, Part 2*; Patai, S., Ed., Wiley: New York, 1982; Chapter 25.
(14) Cordell, G. A. *Introduction to Alkaloids: A Biogenetic Approach*; Wiley: New York, 1981; Chapter 8.
(15) (a) Larsen, S. D.; Grieco, P. A.; Fobare, W. F. *J. Am. Chem. Soc.* **1986**, *108*, 3512, and references cited therein. (b) Doedens, R. J.; Meier, G. P.; Overman, L. E. *J. Org. Chem.* **1988**, *53*, 685.
(16) Hiemstra, H.; Fortgens, H. P.; Speckamp, W. N. *Tetrahedron Lett.* **1985**, *26*, 3155.
(17) (a) Flann, C. J.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 6115. (b) Speckamp, W. N. *Recl. Trav. Chim. Pays-Bas* **1981**, *100*, 345, and references cited therein.

Generalized Valence Bond Description of Multiple Bonds

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Recently, we have reported on a number of generalized valence bond (GVB) calculations[1-4] for multiple bonds which have employed the standard strongly orthogonal and perfect-pairing (SOPP) approximations,[5] i.e., the GVB-PP method. In these calculations for CO_2, C_2F_2, benzene, and CO, we have found that the usual description of multiple bonds in terms of σ and π bonds is energetically less favorable than a description in terms of "bent bonds".

The physical significance of the results of C_2F_2 has been challenged[6,7] however on two grounds. The first criticism is that conclusions based upon the results of GVB-PP calculations may not be valid because the restrictive nature of the SOPP approximation to the full GVB wave function,[8] the most general wave function interpretable within an independent particle (IP) picture, may produce artifacts. A second criticism is that the valence bond approach itself is too restrictive and that a more general wave function may demonstrate that the σ,π description is the "correct" description of multiple bonds.

These are certainly important points which must be addressed before the validity and utility of the "bent bond" (Ω-bond) description can be fully assessed. In order to resolve the first point, we carry out the *first* full GVB calculations for multiple bonds (i.e., IP calculations which do not invoke either the perfect pairing or strong orthogonality restrictions). We deal with the second criticism immediately, because it is the easier to examine.

For a wave function more general than the valence bond wave functions above, the question of whether the "bent bond (Ω-bond)" or the σ,π bond description is better is not even meaningful. GVB-CI calculations[6] on C_5F_4 or full valence CI (FVCI) calculations[7] on C_2F_2 cannot address this question because the wave functions cannot be interpreted unambiguously in terms of either

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‡ University of Pennsylvania.

(1) Messmer, R. P.; Schultz, P. A.; Tatar, R. C.; Freund, H.-J. *Chem. Phys. Lett.* **1986**, *126*, 176.
(2) Messmer, R. P.; Schultz, P. A. *Phys. Rev. Lett.* **1986**, *57*, 2653.
(3) Schultz, P. A.; Messmer, R. P. *Phys. Rev. Lett.* **1987**, *58*, 2416.
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(5) Hay, P. J.; Hunt, W. J.; Goddard, W. A., III *J. Am. Chem. Soc.* **1972**, *94*, 8293. Hunt, W. J.; Hay, P. J.; Goddard, W. A.; III *J. Chem. Phys.* **1972**, *57*, 738. Bobrowicz, F. W.; Goddard, W. A., III In *Modern Theoretical Chemistry*; Schaefer, H. F., III, Ed.; Plenum Press: New York, 1977, Vol. 3, Chapter 4.
(6) Carter, E. A.; Goddard, W. A., III *J. Am. Chem. Soc.* **1988**, *110*, 4077.
(7) Bauschlicher, C. W., Jr.; Taylor, P. R. *Phys. Rev. Lett.* **1988**, *60*, 859. The FVCI, SOGVB, and FVMCSCF results quoted are combinations of σ,π and bent bond descriptions.

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