of the carboxylic acid 14 with N^{im}-Boc-L-His-L-Ala-OBu^t (15)[11] provided desacetamido P-3A in its fully protected form 16 (80%).[12] Acid-catalyzed deprotection provided 2 [90%, $[\alpha]^{22}_D$ −13.3 (c 0.15, CH_3OH), $[\alpha]^{22}_D$ −18.0 (c 0.15, 0.1 N HCl)].

(11) Prepared from N^{α}-CBZ-L-histidine (17) and L-alanine *tert*-butyl ester hydrochloride (18) by the following reactions: (i) 17, Boc_2O, aq NaOH (86%); (ii) 18, EDCI, HOBt, DMF (51%); (iii) H_2, 10% Pd–C, CH_3OH (90%). The attempts to use the corresponding methyl ester of 15 resulted in significant amounts of intramolecular lactam formation with diketopiperazine formation.

(12) EDCI = [3-(dimethylamino)propyl)]ethylcarbodiimide, HOBt = 1-hydroxybenzotriazole.

The examination of the properties of 2 as well as the extension of this work to the synthesis of P-3A, pyrimidoblamic acid, and the bleomycins are in progress and will be reported in due course.

Acknowledgment. We gratefully acknowledge the financial support of the National Institute of Health (CA41986 and 42056).

Supplementary Material Available: Full experimental details and characterization of 9–13, 15–16, and 2 (11 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Spontaneous Free-Radical Formation in Reactions of *m*-Chloroperbenzoic Acid with *C*-Phenyl-*N*-*tert*-butylnitrone (PBN) and 3- or 4-Substituted PBN's

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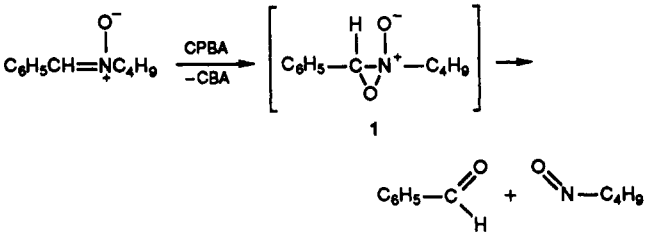
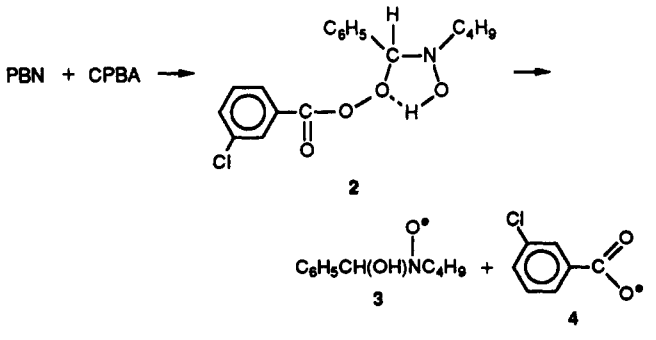
Summary: A molecular reaction between *m*-chloroperbenzoic acid and *C*-phenyl-*N*-*tert*-butylnitrone (PBN) produces significant amounts of aminoxyl radicals assigned to the *m*-chlorobenzoyloxyl adduct of PBN and benzoyl-*tert*-butylaminoxyl.

m-Chloroperbenzoic (CPBA) acid is commonly used as a reagent for producing epoxides from olefins.[1] *m*-Chlorobenzoic acid (CBA) is the only other product formed. In an analogous reaction with *C*-phenyl-*N*-*tert*-butylnitrone (PBN), the compounds benzaldehyde and 2-methyl-2-nitrosopropane might be produced since the oxazirane *N*-oxide 1 is not expected to be stable:



1

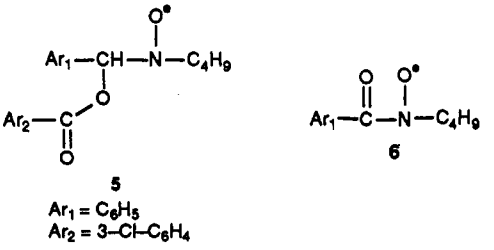
However, if a precursor molecular addition product is formed having the structure of the hydroxylamine of the peroxyl adduct 2 this addition product might be expected to produce aminoxyl radicals spontaneously by an internal redox reaction:



2

3 4

The products would be the hydroxyl adduct of PBN 3 and the *m*-chlorobenzoyloxyl radical 4. The latter should be readily trapped by PBN[2] to give the spin adduct 5.

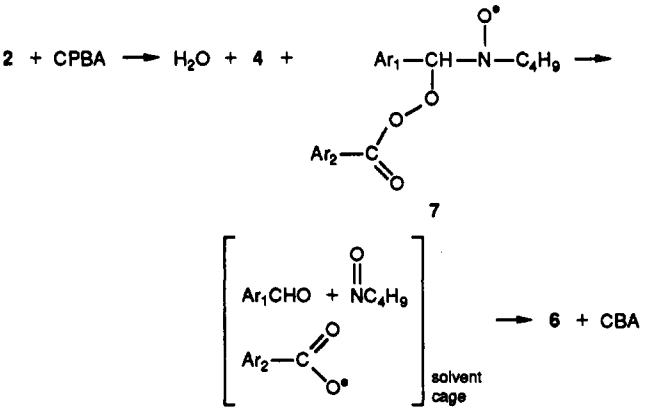


5

$Ar_1 = C_6H_5$
$Ar_2 = 3\text{-}Cl\text{-}C_6H_4$

6

Another mechanism involving oxidation of 2 before internal disproportionation is possible:



7

solvent cage

If the reaction within the solvent cage is very efficient then approximately equal amounts of 5 and 6 might be expected. Decomposition of peroxyl adducts is known to produce acyl aminoxyls 6 and oxyl adducts of PBN 5.[3] The benzoyloxyl adduct of 2-methyl-2-nitrosopropane (MNP) is not known. In general, oxyl adducts of MNP are not persistent aminoxyls at room temperature.

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‡ Support by NIH Grant No. RR05517, awarded by The National Center for Research Resources.

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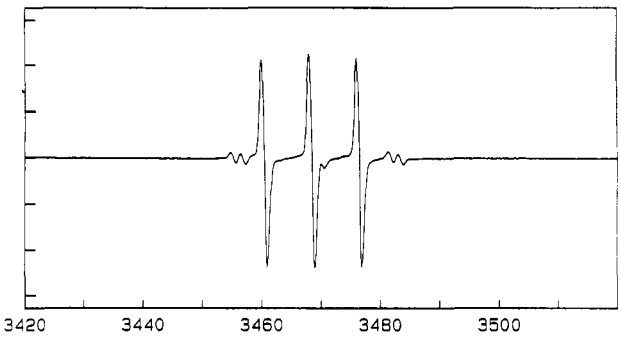


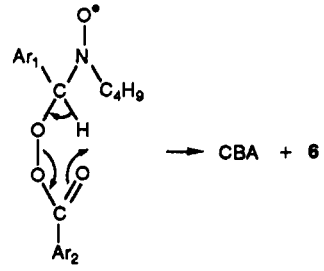
Figure 1. EPR spectrum obtained in benzene from 0.02 M PBN plus 0.01% CPBA in the absence of air and light at room temperature.

Table I. EPR Hyperfine Splitting Constants of 5 and 6[a]

R	a^N	a_β^H	g-value	a^N	g-value
		Benzene			
p-CH_3O	13.43	1.73	2.006 35	8.36	2.006 72
p-CH_3	13.36	1.72	2.006 29	8.12	2.006 75
H	13.28	1.65	2.006 35	8.00	2.006 84
p-Br	13.21	1.56	2.006 28	7.87	2.006 76
m-Br	13.16	1.52	2.006 41	7.77	2.006 89
		Acetonitrile			
p-CH_3O	13.61	1.90	2.006 23	8.50	2.006 69
p-CH_3	13.52	1.88	2.006 26	8.32	2.006 71
H	13.46	1.84	2.006 21	8.12	2.006 73
p-Br	13.41	1.75	2.006 26	7.97	2.006 71

[a] In gauss ± 0.05 G; error in g-value = ±0.000 07.

There is also the possibility that the reaction of **7** to produce **6** and CBA is concerted:



Thus, when 0.1% CPBA (Aldrich 55% purity) in benzene is mixed with 0.02 M PBN in the dark the EPR spectrum in Figure 1 is observed. Analysis of the spectrum shows that **5** and **6** are the major initial aminoxyls formed. The same reaction occurs with 3- and 4-substituted PBN's and in all cases the same major products are produced, namely the benzoyloxyl adduct of the substituted PBN and the substituted acyl aminoxyl (see Table I).

The normal substituent effect is found for both **5**[4,5] and **6**;[6] i.e., both the nitrogen hyperfine splitting constant (hfsc) and the β-H hfsc decrease with increasing electron-withdrawing capability of the aryl substituent. The same aminoxyl products (see Table I) and the same trends in the effect of substituent are found in acetonitrile. The change in g-value is more difficult to discern because of the large error inherent in measuring g-values in a mixture EPR spectrum.

With time another set of three peaks is clearly evident growing steadily in intensity. Since this aminoxyl always gives the same N-hfsc regardless of the substituent on the PBN derivative, namely a^N = 15.44 G, this species is assigned to di-*tert*-butylaminoxyl (see Figure 2).

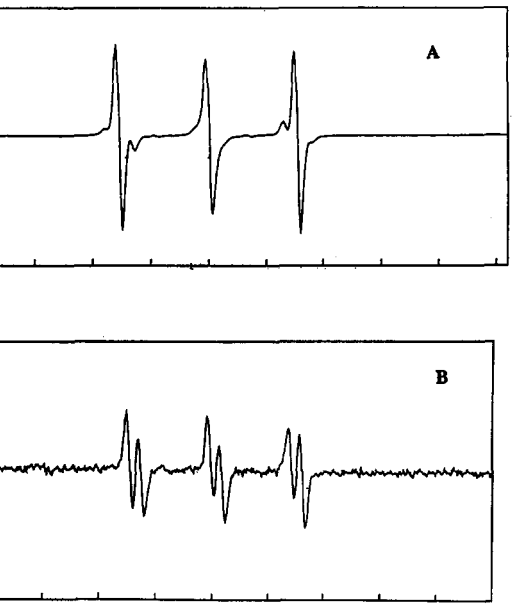


Figure 2. EPR spectrum in benzene (A) 15 h and (B) 5 days after the spectrum in Figure 1 was obtained under the same conditions.

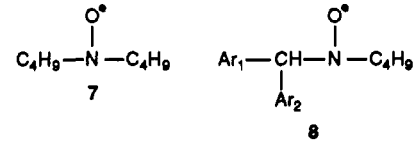
Table II. EPR Hyperfine Splitting Constants of 8 in Benzene[a]

R	a^N	a_β^H	g-value
p-CH_3O	14.47	2.03	2.006 12
p-CH_3	14.44	2.20	2.006 12
H	14.40	2.08	2.006 13
p-Br	14.40	2.07	2.006 11
m-Br	14.36	2.13	2.006 06

[a] In gauss ± 0.05 G; error in g-value = ±0.000 07.

Table III. Yield of Aminoxyls with Substituent and Solvent

	benzene (all × 10^{-6} M)		acetonitrile (all × 10^{-6} M)	
R	5	6	5	6
p-CH_3O	0.44	0.86	0.98	0.23
p-CH_3	0.23	0.69	0.24	0.91
H	2.0	16	0.72	0.57
p-Br	0.19	1.0	0.13	0.14
m-Br	0.10	0.54		



After 5 days in benzene the spectrum consists solely of a triplet of doublets with larger values for the N- and β-H hfsc's than for the comparable benzoyloxyl adducts **5** (see Table II). This spectrum is tentatively assigned to the *m*-chlorophenyl adduct of PBN. *m*-Chlorophenyl radicals would be produced by the decarboxylation of the *m*-chlorobenzoyloxyl radical.

The amounts of aminoxyls formed depend on the substituent but in a peculiar way, namely both electron-donating as well as electron-withdrawing substituents lead to a decrease in the yield of radicals. The one exception is **5a** in acetonitrile (see Table III). Based on the amount

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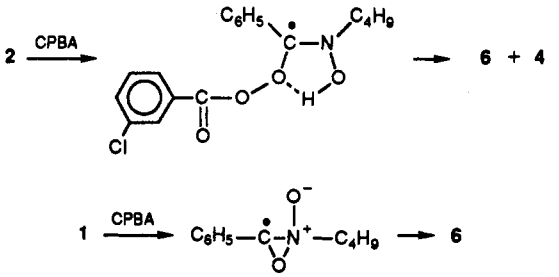
of PBN or substituted PBN present the aminoxyl yield is in the range of 0.05–7.8%. PBN in benzene appears to give the highest yield. In acetonitrile the concentration of **5** exceeds **6** (except for *p*-BrPBN) whereas in benzene the reverse is true. When water is added to acetonitrile the substituted PBN's are less soluble. However, the acyl aminoxyl **6** is formed in 1:1 acetonitrile and water, e.g., for R = H, *p*-Br, a^N = 8.25 and 8.09 G, respectively. When samples of PBN and *m*-chloroperbenzoic acid are mixed in the cold (200 K) no aminoxyl radical reaction is found. The first EPR signal is produced when the temperature is increased to 263 K. Maximum intensity is reached at 313 K for **5** and 293 K for **6**. The greater sensitivity of **6** to heat is indicated by the complete disappearance of its signal by 320 K. The formation of **5** and **6** does not depend on light (all experiments were run in the dark) or air (all experiments were run under nitrogen). The presence of oxygen broadens the lines, but the same mixture of **5** and **6** appears to be present. A 0.02 M concentration of PBN was able to detect the presence of as little as 0.001% (5.79×10^{-5} M) CPBA in acetonitrile. With α-D PBN (C_6H_5C-$DN(O)C_4H_9$) initial formation of **5** and **6** is slightly slower than for normal PBN. The observed isotope effects on the rate of formation of **5** and **6** were 2.56 and 2.45, respectively.

The precise mechanism of aminoxyl radical production in the reaction of *m*-chloroperbenzoic acid with *C*-phenyl-*N*-*tert*-butylnitrone is still not clear. Evidence indicates that a "molecule-induced" free-radical reaction not greatly affected by polar substituents or polarity of solvent is occurring. A small isotope effect with α-D PBN indicates bond breaking of the benzylic carbon–hydrogen bond is involved prior to or in the rate-determining step. No evidence for the intermediacy of **3** is found although small amounts of this aminoxyl may be undetected in a mixture spectrum. Thus, a combination of concerted and intermolecular redox reactions is indicated. If there is any significance to the fact that the estimated isotope effects for the initial formation of **5** and **6** are the same it would seem that the production of these aminoxyls may depend on the same benzylic carbon–hydrogen bond-breaking step. The reactions which accommodate this possibility are as follows:



Further investigations are underway since it is important to know whether the reaction between acyl hydroperoxides (peracids) and nitrones is general. This molecular reaction may have significant impact on the use of spin traps in biological systems.

Acknowledgment. The authors recognize the financial support for a studentship for C.-R.L. provided by the National Taiwan University and facilitated by Prof. T.-I. Ho. Assistance in this work from Dr. Y. Kotake is also gratefully acknowledged.

Supplementary Material Available: Experimental details (1 page). Ordering information is given on any current masthead page.

$TiCl_4$-Mediated Reactions of Alkyl Azides with Cyclic Ketones

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Summary: The reaction of cyclic ketones with alkyl azides to afford N-alkyl lactams can be effected by $TiCl_4$.

The Schmidt reaction of ketones with hydrazoic acid is an important method for the preparation of N-unsubstituted lactams.[1] Since alkyl azides do not react under standard Schmidt conditions,[2] a variety of other methods have been reported for the formal insertion of a primary amine adjacent to a ketone. These include the reactions of ketones with *N*-[(arylsulfonyl)oxy]amines,[3] the reactions of substituted amines with cyclopropanones (limited to β-lactam synthesis)[4] and multistep methods involving oxaziridine[5] or nitrone[6] intermediates. Clearly, given the ready availability of a wide variety of alkyl azides, the extension of the Schmidt reaction to those reactants would be a welcome development. We recently reported that the *intramolecular* Schmidt reaction of keto azides occurs readily under protic or Lewis acid conditions to give bicyclic lactams.[7] In this paper, we consider the problem

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