Chemistry of Singlet Oxygen. 31. Low-Temperature Nuclear Magnetic Resonance Studies of Dye-Sensitized Photooxygenation of Imidazoles: Direct Observation of Unstable 2,5-Endoperoxide Intermediates[1a]

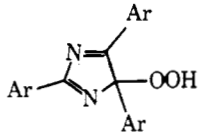
Hong-Son Ryang and Christopher S. Foote*

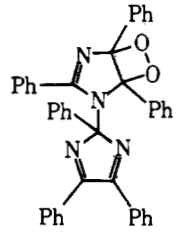
Contribution from the Department of Chemistry, University of California, Los Angeles, California 90024. *Received May 29, 1979*

Abstract: Low-temperature nuclear magnetic resonance studies of the dye-sensitized photooxygenation of imidazoles, including histidines, provide direct evidence for the formation of 2,5-endoperoxides, stable only at low temperatures. The intermediates have been shown to undergo several subsequent reactions depending on the substituents. In two cases, but not in three others, the initial adduct loses oxygen (partially singlet) to regenerate starting material.

Dye-sensitized photooxygenation of amino acid residues has been extensively studied; in many enzymes, photooxidative damage to histidine residues causes loss of activity.[1b-d,2] Mechanistic studies strongly indicate that the reaction of histidine involves singlet oxygen[3] and the target of the oxidation is the imidazole ring of the histidine residue.[4] However, the initial product of oxidation still remains to be identified because of its instability and ready further reaction.

Earlier studies of the photooxygenation of histidine have shown that aspartic acid and urea are formed as final products.[4a,b] Subsequently, isolation of 17 oxidation products has been demonstrated, indicating the high susceptibility of the intermediates to attack by nucleophiles.[4c] It has been reported that 2,4,5-triarylimidazole gives the corresponding 4-hydroperoxy derivative which cleaves in a chemiluminescent reaction to afford the C_4–C_5 bond fission product.[5, 17] Recently a dioxetane has been obtained from bis(2,4,5-triphenyl)imidazoyl.[6]

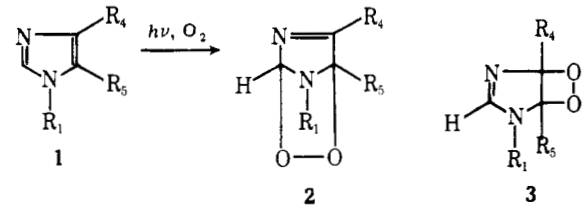




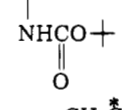
We now report low-temperature NMR studies of dye photosensitized oxygenation of imidazoles (**1a–g**) and the first observation of 2,5-endoperoxides (**2**) as initial oxidation products.

Results and Discussion

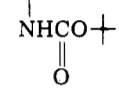
4(5)-Methylimidazole (**1f**) and *N*-α-Boc-L-histidine methyl ester (**1g**) were used as model compounds. Since it is well known that N-unsubstituted imidazoles can exist in two tautomeric structures,[7] the photooxidation of the corresponding *N*-methyl derivatives was also studied and comparison of NMR data for **1f** and **1g** and their *N*-methyl derivatives was used to elucidate questions of tautomeric equilibrium. Boc-L-1-methyl- (**1d**) and 3-methyl- (**1e**)histidine methyl esters were prepared as described in the Experimental Section. NMR-compatible solvents, such as Freon 11-chloroform-*d* (2:1, v/v, solvent A), Freon 11-acetone-d_6 (1:1, v/v, solvent B), or acetone-d_6 (solvent C), were chosen for the reaction because it has been demonstrated that the oxidation intermediates are susceptible to the attack of nucleophiles such as water and methanol.[4b,4c] Tetraphenylporphine (TPP) or methylene blue (MB) was used as a sensitizer. Each sample was prepared in an NMR tube and irradiated. During irradiation, oxygen was bubbled through the solution. NMR spectra were taken just after photooxidation.



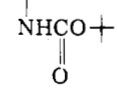
a: $R_1 = CH_3$ $R_4 = R_5 = H$
b: $R_1 = CH_3$ $R_4 = Me$, $R_5 = H$
c: $R_1 = CH_3$ $R_4 = H$, $R_5 = Me$
d: $R_1 = CH_3$ $R_4 = —CH_2\overset{*}{C}HCO_2Me$ (L), $R_5 = H$



e: $R_1 = CH_3$ $R_4 = H$, $R_5 = —CH_2\overset{*}{C}HCO_2Me$ (L)



f: $R_1 = H$, $R_4 = Me$, $R_5 = H$
g: $R_1 = H$, $R_4 = CH_2\overset{*}{C}HCO_2Me$, $R_5 = H$



***N*-Methylimidazoles (1a–c).** The photosensitized oxygenation of *N*-methylimidazoles (**1a–c**) was carried out both in solvent A with TPP as a sensitizer at −78 °C and in solvent B with MB as a sensitizer at −100 °C. After irradiation, NMR spectra were taken at the irradiation temperature. In all cases, the reactions were complete in 5 min under both conditions and gave only one product. Longer irradiation times did not cause any further oxidation.

The chemical shifts of the products (**2a–c**) as well as those of starting materials **1a–c** are shown in Table I. The results are reasonably explained by assuming that the oxidation products are 2,5-endoperoxides. An alternative possibility, the formation of dioxetane **3**, could be eliminated because **3** should not show any imino methyl signals (δ ca. 2.1) when R_4 or R_5 is a methyl group and should have a formamidino proton at C_2 (δ ca. 8.1)

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Table I. ^{1}HNMR Data for **1a–c** and **2a–c**

compd	conditions[a]	sens.	decomp T, °C	chemical shifts (δ), ppm[b] N-Me	C_2-H	R_4	R_5
1a	A			3.71	7.44	7.03	6.89
2a	A	TPP	−50	2.38	6.23	8.12	5.46
1b	A			3.60	7.30	2.16	6.57
	B			3.71	7.44	2.13	6.79
2b	A	TPP	−30	2.40	6.11	2.22	5.32
	B	MB		2.24	6.20	2.10	5.66
1c	A			3.52	7.36	6.70	2.16
	B			3.54	7.38	6.50	2.12
2c	A	TPP	−60	2.28	6.20	8.00	1.70
	B	MB		2.16	6.47	8.12	1.62

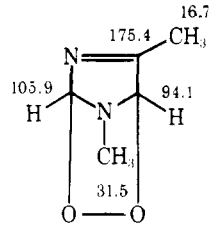
[a] A: solvent $CDCl_3/CFCl_3$ = 1/2 (v/v) at −78 °C. B: solvent $(CD_3)_2CO/CFCl_3$ = 1/1 (v/v) at −100 °C. [b] Internal standard: $CHCl_3$ (δ 7.25 ppm) in A; $(CH_3)_2CO$ (δ 2.05 ppm) in B.

Table II. ^{1}HNMR Data for **1d–e** and **2d–e**[a]

compd	chemical shifts (δ), ppm (mult, J, Hz)[b] N-Me	C_2-H	C_4-H	C_5-H	amino acid moiety $-CH_2-$	−CH−	>NH	$-CO_2Me$	CO_2+
1d	3.62	7.33		6.64	3.05 (m)	4.52 (m)	5.86 (d, 7.0)	3.71	1.43
2d[c]	2.40	6.12		5.38	3.08 (m)	4.71 (m)	5.92 (d, 7.0)[e] and 5.87 (d, 8.0)	3.75	1.46
1e	3.58	7.40	6.79		3.10 (m)	4.52 (m)	5.15 (d, 7.5)	3.75	1.42
2e[d]	2.34	6.28	8.07		2.52 (m)	4.60 (m)	5.70 (d, 7.0)[f] and 5.60 (d, 7.5)	3.82	1.45

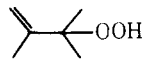
[a] In $CDCl_3/CFCl_3$ = 1/2 (v/v) at −78 °C, sens. TPP. [b] Internal standard $CHCl_3$, δ 7.25 ppm. Decomp at −50 °C. [d] Decomp at −60 °C. [e] Signal ratio 1:1. [f] Signal ratio 1:1.

in all cases, whereas, for example, **2b** showed an imino methyl group on C_4 (δ 2.22 in solvent A and 2.10 in solvent B) and a tertiary proton on C_2 (δ 6.11 in solvent A and 6.20 in solvent B). The formation of 2,5-endoperoxides as oxidation intermediates is confirmed by the ^{13}C NMR spectrum of **2b,** which is the most stable of the endoperoxides. The ^{13}C NMR spectrum of **2b** at −78 °C showed peaks at δ (CD_2Cl_2, δ 53.7 ppm internal standard) 16.7 (q, C_4-*CH_3), 31.5 (q, N-*CH_3), 94.1 (d, *C_5), 105.9 (d, *C_2), and 175.4 (s, *C_4=N), which were consistent with the results of the ^{1}H NMR spectrum and reasonably assigned on the basis of structure **2b.**



2b

It was found that when the NMR probe temperature was increased, **2a** (>−50 °C) and **2b** (>−30 °C) liberated oxygen quantitatively to regenerate the original imidazoles (**1a–b,** respectively), whereas **2c** did not show this reversibility but decomposed to give a complicated reaction mixture. The stability of the products decreases in the order **2b** > **2a** > **2c,** as shown in Table I. The addition of excess tetramethylethylene (TME) to decomposing solutions of **2a** and **2b** resulted in the formation of the singlet oxygen product, 2,3-dimethyl-3-hydroperoxy-1-ene (**4**), detected after reduction to the alcohol



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by NMR in 27 and 20% respectively.[18] Previously, thermal formation of singlet oxygen from the retro-Diels–Alder reaction of the peroxides of anthracences and pyrroles has been reported.[9] Thus **2a** and **2b** seem to be further examples of the formation of $^1O_2$ on decomposition of cyclic peroxides.

Compounds 1d and 1e. The photooxygenation of **1d** and **1e** in solvent A with TPP as a sensitizer was carried out at −78 °C. The NMR spectra of the products (**2d** and **2e**) as well as those of **1d** and **1e** taken at −78 °C are shown in Table II. No other signals were observed at −78 °C. Close similarities in chemical shifts of the ring protons of **2d** to those of **2b** and of **2e** to those of **2c,** and the higher chemical shift of the C_5-methylene group of **2e,** indicating sp^3 hybridization of the C_5 carbon, clearly suggest that the oxidation products are 2,5-endoperoxides **2d** and **2e,** respectively.

The observation of two different chemical shifts of the amino protons of the products from each starting material, shifting to higher fields with increased temperature, is attributed to the formation of two diastereomers owing to approach of oxygen from the two sides of the ring: one product results from attack from the top of the ring, the other from the bottom. Neither of the sets of products showed any thermal loss of oxygen but gave very complicated degradation mixtures on warming above −50 °C.

Photooxygenation of 4-Methylimidazole 1f. As mentioned previously, N-unsubstituted imidazoles exhibit tautomerism in solution.[7] At room temperature, the NMR spectrum of **1f** showed only averaged signals of the two tautomers.[10] However, by using low temperature NMR spectra, the ratio of **1f** and **1f'** could be measured in solvent B and solvent C (Table III). (Because of the low solubility of **1f** and products, solvent A was not used.) In solvent B (−100 °C) the ratio of **1f**/**1f'** is 2.3/1, whereas in solvent C (−90 °C) it is 1.8/1.

The photooxygenation of **1f** (**1f'**) was carried out in solvent B at −100 °C and in solvent C at −90 °C with MB as a sensitizer. After complete oxidation, the NMR spectra of the solutions showed new signals corresponding to **2f** and **2f'** as shown in Table III. The assignments of the signals for the products are based primarily on comparison with data in Tables I and II. In solvent B at −100 °C no other signals were obtained. However, the signals corresponding to **2f'** completely

Table III. ^{1}HNMR Data for **1f** (**1f'**) and **2f** (**2f'**)

compd	conditions[b]	Ratio **1f/1f'** or **2f/2f'**	sens.	decomp *T*, °C	chemical shifts (δ), ppm[a] N-H	C_2-H	C_4-Me	C_5-H
1f	B	2.3/1			14.40	7.67	2.20	6.76
1f'					10.20	7.82	2.10	7.00
1f	C	10/5.5			5.08	7.82	2.20	6.91
1f'					8.55	7.88	2.13	7.16
2f	B	4/3	MB	−30	4.35	6.56	2.13	5.97
2f'				−80	4.45	6.64	1.74	7.97
2f	C	2.7/1	MB	−40	4.00	6.84	2.13	6.18
2f'				−85	4.56	6.82	1.76	8.13

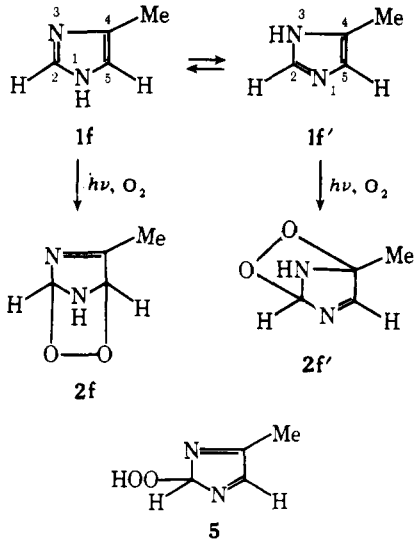
[a] Internal standard $(CH_3)_2CO$, δ 2.05 ppm. [b] B: solvent $(CD_3)_2CO/CFCl_3$ = 1/1 (v/v) at −100 °C. C: solvent $(CD_3)_2CO$ at −90 °C.

Table IV. ^{1}H NMR Data for **1g** and **2g**

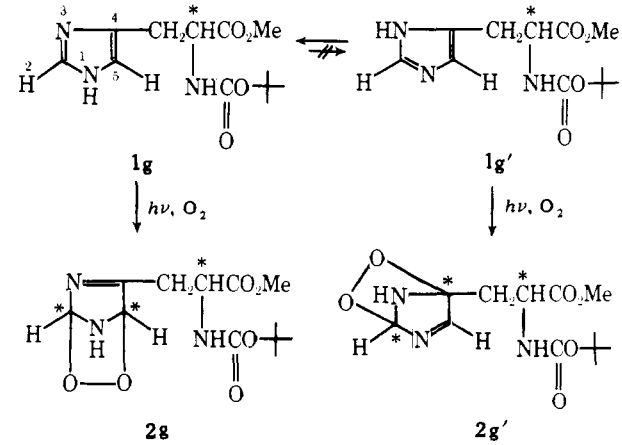
compd	conditions[b]	chemical shifts (δ), ppm (mult, *J*, Hz)[a] N-H	C_2-H	C_5-H	amino acid moiety $-CH_2-$	−CH−	>HN	$-CO_2Me$	CO_2+
1g	B (−100 °C)	12.75	7.72	6.99	2.94 (m)	4.28 (m)	7.13 (d, 8.5)	3.58	1.33
1g	C (−90 °C)	11.20	7.80	7.08	2.95 (m)	4.36 (m)	7.27 (d, 8.4)	3.60	1.30
2g[c]	B[e] (−100 °)	4.48	6.64	6.10	3.00 (m)	4.60 (m)	6.75 (d, 7.5)	3.65	1.35
		4.43	6.64	6.15	3.00 (m)	4.50 (m)	6.70 (d, 7.5)	3.65	1.35
	B (−78 °C)	4.33	6.60	6.10	3.00 (m)	4.60 (m)	6.50 (d, 7.5)	3.65	1.35
		4.30	6.57	6.10	3.00 (m)	4.50 (m)	6.45 (d, 7.5)	3.65	1.35
2g[d]	C[e] (−90 °C)	4.57	6.85	6.27	3.05 (m)	3.65 (m)	6.81 (d, 8.0)	3.65	1.35
						3.63 (m)	6.73 (d, 8.3)	3.63	1.35

[a] Internal standard $(CH_3)_2CO$, δ 2.05 ppm. [b] B: solvent $(CD_3)_2CO/CFCl_3$ = 1/1 (v/v). C: solvent $(CD_3)_2CO$. [c] Decomp at −45 °C. [d] Decomp at −30 °C. [e] Sens. MB.

disappeared at −80 °C with the appearance of new signals at δ (ppm) 12.11 (1 H, s), 8.08 (1 H, s), 6.54 (1 H, s), and 2.37 (3 H, s) which disappeared at −50 °C. In solvent C at −90 °C, several minor signals besides those of **2f** and **2f'** were observed, and the decomposition of **2f'** was not accompanied by the formation of clear new signals. Peroxide **2f** was still stable at the decomposition temperature of **2f'**. The signal at δ 12.11 ppm is probably assigned to an -OOH proton and suggests a strong intermolecular N-HO hydrogen bond as observed in the case of lophyl hydroperoxide.[5b-c] The results indicate the transformation of the less stable peroxide **2f'** to a further reaction intermediate, probably the corresponding hydroperoxide **5**.[11] Neither **2f** nor **2f'** showed thermal deoxygenation, indicating the important role of the N-H proton in the reactivity of the intermediate and suggesting that proton transfer of the N-H proton to oxygen is a more facile path than loss of oxygen.



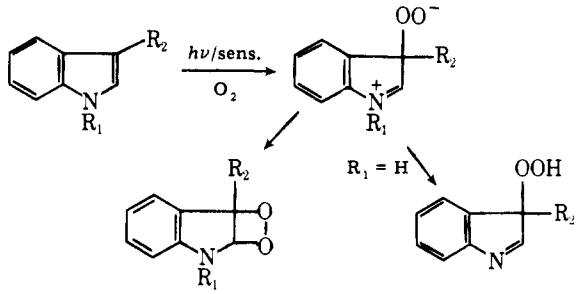
The Photooxygenation of *N*-α-Boc-L-histidine Methyl Ester 1g. The NMR spectrum of **1g** in solvent B at −100 °C or in solvent C at −90 °C showed only two ring protons and one N-H proton (Table IV). The results indicate either that tautomerism is too rapid to be measured by NMR spectroscopy at these temperatures, or that one tautomer is predominant under the conditions. After complete photooxygenation of **1g** in solvent B (−100 °C) and solvent C (−90 °C) with MB as a sensitizer, the NMR spectra showed new signals as shown in Table IV. No other signals were observed. The similarity of the chemical shifts of the ring protons to those in **2b, 2d,** and **2f** suggests that the products are the two diastereomers of the 2,5-endoperoxide of **1g,** as observed in the case of the corresponding *N*-methyl derivatives of **1g.**



Both tautomeric forms of histidine have been observed by ^{13}C NMR and it has been concluded that the 1-H tautomer is the predominant form in basic solutions.[7c] Our observation that no **2g'** was obtained under the conditions might be due to the predominance of the 1-H tautomer **1g** in both solvent systems.

Discussion

With regard to the mechanism of photooxygenation of indoles[12] and enamine[13] systems, it has been proposed that the reaction initially involves a zwitterionic peroxide which is transformed into a dioxetane or, when an N-H proton is present, into the iminohydroperoxide. The formation of lophyl hydroperoxide from lophine[5b,5c] implied the possibility of a similar mechaism for the triphenylimidazole system. However, the observed products of photooxidation of **1f** (**1f'**) and **1g** clearly indicate that, even in the case of *N*-unsubstituted imidazoles, a 2,5-endoperoxide is the first stable product, whatever the initial step is.



Although our results provide evidence for the intermediacy of 2,5-endoperoxides, the reactivity of the intermediates varies, as with other cyclic peroxides,[14] and seems to be dependent on the substituents on the ring. From the results above, the endoperoxides from 4-alkylimidazoles (**2b, 2d,** and **2f**) are more stable than those from the corresponding 5-alkyl derivatives (**2c, 2e,** and **2f'**) respectively. The results also indicate that N-H imidazoles give less stable intermediates than the corresponding *N*-methyl derivatives. Peroxides **2a** and **2b** undergo "pyrolysis" to liberate singlet oxygen, whereas none of the other peroxides gave this reaction. The higher temperature required for reaction of **2b** compared with **2a** might be attributed to the stabilizing effect of the C_4-methyl group on **2b.** The failure of the reverse reaction in the case of **2c** and the lower stability of **2c** compared with **2a** shows there is an alternate pathway which requires less activation energy than the reverse Diels–Alder, perhaps through an ionic intermediate stabilized by the C_5-methyl substituent. The lower stability of **2f'** than **2f** and the probable formation of **5** from **2f'** are consistent with the instability of **2c** and might be explained by the facile formation of a zwitterion intermediate stabilized by the C_5-alkyl group, followed by N-H proton transfer to oxygen. The failure of the histidines (**2d, 2e,** and **2g**) to give the reverse Diels–Alder may be due in part to nucleophilic attack of the amino group on the oxidized rings.[4c]

Experimental Section

General. Boiling points and melting points are uncorrected. Nuclear magnetic resonance spectra were determined on a Bruker WP-200 spectrometer. Mass spectra were determined on an AEI MS-9 mass spectrometer. 1-Methylimidazole (Aldrich) was purified by distillation and stored over molecular sieves (Linde 4A). 4(5)-Methylimidazole (Aldrich) and *N*-α-Boc-L-histidine methyl ester (Calbiochem) were recrystallized from benzene and stored in a desiccator containing P_2O_5 under vacuum. 3-Methyl-L-histidine (Sigma), 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile (Boc-ON, Aldrich), tetraphenylporphine (TPP, Aldrich), and methylene blue (MB, Matheson, Coleman and Bell) were used as received. 1,4- and 1,5-dimethylimidazoles (**1b** and **1c**) were synthesized from 4(5)-methylimidazole (**1f**) following the method of Windaus and Knoop.[15] Separation of the isomers was accomplished without loss by using column chromatography on neutral alumina (eluant, chloroform:benzene, 8:2). The first fraction is **1b,** followed by **1c.** These compounds were purified by distillation under reduced pressure and stored in a refrigerator over molecular sieves.

***N*-α-Boc-1-methyl-L-histidine Methyl Ester (1d).** A mixture of Boc-L-histidine methyl ester (269 mg, 1 mmol) and MeI (6 mL) was stirred for 24 h at room temperature. Evaporation of unreacted MeI gave a mixture of 1-methyl and 3-methyl quaternary salts of **1d** in a quantitative yield. The NMR spectrum of the mixture showed signals at δ ($CDCl_3$, Me_4Si) 1.40 (s, 18 H, *t*-Bu), 3.35 (m, 4 H, $-CH_2O$), 3.80 (s, 6 H, ester Me), 3.97 (s, 6 H, N^+-Me), 4.03 (s, 6H, N^+-Me), 4.60 (m, 2 H, CH), 5.83 (broad, 2 H, amide-H), 7.36 (2 H, C_4-H and C_5-H), 8.89 (1 H, C_2-H), and 9.55 (1 H, C_2-H). The mixture was used without further purification. A solution of the salts and K_2CO_3 (151 mg, 1.1 mmol) in dry acetone was stirred for 24 h at room temperature and filtered. The filtrate was concentrated to dryness and the residue was taken up in chloroform. The insoluble material was removed by filtration. The filtrate was evaporated to dryness. The NMR spectrum of the crude mixture showed the formation of *N*-α-Boc-L-1-methylhistidine methyl ester (**1d,** ~30%) together with the corresponding 3-methyl derivative (**1e,** ~10%). The product **1d** was purified by thin-layer chromatography on silica gel (EM reagents type 60 F254) at 4 °C using chloroform–acetonitrile (70/30, v/v) as the eluant (R_f 0.4); mass spectrum *m/e* 283.1524 (M^+, calcd for $C_{13}H_{21}N_3O_4$, 283.1532), 70 eV, *m/e* (relative intensity) 283 (8.9), 227 (9.5), 210 (33), 168 (22), 166 (48), 150 (15), 124 (26), 96 (77), and 95 (100).

Compound **1e** could not be isolated because of decomposition under the conditions and was synthesized independently as follows.

Synthesis of *N*-α-Boc-L-3-methylhistidine Methyl Ester (1e). L-3-Methylhistidine methyl ester was prepared from 3-methylhistidine following the method of Behrens and du Vigneaud.[16] To a solution of the ester (30 mg, 0.16 mmol) in Et_3N (24.9 mg, 0.25 mmol) in dioxane–water (14 mL, 2/1, v/v) was added Boc-ON (48.5 mg, 0.20 mmol) at room temperature. The mixture was stirred at room temperature for 12 h. Evaporation of the solvents under reduced pressure gave a crude reaction mixture. The NMR spectrum showed the major product to be **1e** (60%). The product was purified by TLC on alumina (Eastman) at 4 °C by using chloroform as the eluant (R_f 0.8); mass spectrum *m/e* 283.1550 (M^+ calcd for $C_{13}H_{21}N_3O_4$, 283.1532) 70 eV, *m/e* (relative intensity) 283 (3.3), 227 (27), 210 (32), 168 (22), 166 (50), 149 (27), 96 (84.7), and 95 (100).

General Procedure for Photooxygenation and NMR Measurement. The compounds were handled under N_2 atmosphere to prevent moisture absorption. Samples were prepared at a concentration of about 10^{-2} M in NMR tubes. TPP or MB were used as sensitizers at a concentration of 10^{-5} M. Three solvent systems were used for the reaction depending on the solubility of the compounds and the stability of the products: Freon 11–chloroform-*d* (v/v, 2:1, solvent A); Freon 11–acetone-d_6 (v/v 1:1, solvent B); and acetone-d_6 (solvent C).

Photooxygenation was carried out by means of a tungsten–halogen DWY lamp (650 W) operated at 70 V and filtered through a solution of K_2CrO_4 (30 g/100 mL, 1 cm). The NMR tube with the mixture irradiated was in a half-silvered Dewar at the temperature as mentioned in the tables. Oxygen was bubbled through the solution during irradiation. Irradiation time depended on the compound, but 5-min irradiation was sufficient to accomplish the reaction in all cases. Longer irradiation did not cause any further reaction.

NMR spectra were taken just after irradiation at the same temperature as the irradiation. As internal standard, the acetone signal (δ 2.05 ppm) in solvent B or C and the chloroform signal (δ 7.25 ppm) in solvent A were used, respectively. For the ^{13}C NMR measurement a solution of **2a** (25 mg) and dichloromethane-d_2 (4 mL) containing TPP (10^{-5} M) was prepared in a NMR tube. The solution was photooxidized for 10 min. The ^{13}C NMR spectrum of **2b** was measured at −78 °C using CH_2Cl_2 (δ 53.6 ppm) as an internal standard and showed signals at δ 16.7 (q, C_4-*CH_3), 31.5 (q, N-*CH_3), 94.1 (d, *C_5), 105.9 (d, *C_2), and 175.4 (s, *C_4). The ^{13}C NMR spectrum of **1b** showed signals at δ (ppm) 13.7 (q, C_4-*CH_3), 33.2 (q, *N*-*CH_3), 116.7 (d, *C_5), 138.7 (s, *C_4), and 137.0 (d, *C_2).

Trapping of Singlet Oxygen with Tetramethylethylene (TME). A solution of **1a** (20 mg) in CH_2Cl_2 (10 mL) containing TPP (10^{-5} M) was photooxidized for 20 min at −78 °C, and TME (50 μL) was added to the solution at −78 °C. The solution was allowed to stand for 1 h at about −50 °C. After addition of excess $NaBH_4$, the solution was warmed slowly to room temperature. 2,3-Dimethyl-3-hydroxy-1-butene[8] was found (27% based on **1a**). The yields were measured by NMR. Filtration followed by evaporation to dryness gave **1a** (100%). (Warming the solution to room temperature without quenching of the hydroperoxide with $NaBH_4$ resulted in the decomposition of **1a.**) Similar treatment of **1b** also gave the alcohol (20%).

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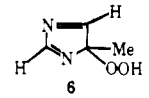

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Interdependence of Solvolysis Rate and Aryl–Aryl Dihedral Angle in a Series of 4-Biphenylyldimethylcarbinyl *p*-Nitrobenzoates

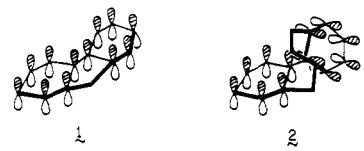
Katsuo Ohkata, Ronald L. Paquette,[1] and Leo A. Paquette*

Contribution from the Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210. *Received May 7, 1979*

Abstract: 4-Biphenylyldimethylcarbinyl *p*-nitrobenzoate and four 2,2′-bridged analogues (1–4 methylene groups) were synthesized and their rates of solvolysis in 80% aqueous acetone determined in order to establish whether there exists in these systems a correlation between kinetic behavior and aryl–aryl dihedral angle. The relative rates at 60.4 °C are as follows: $n = 0$, 1; $n = 1$, 17.6; $n = 2$, 4.3; $n = 3$, 1.8; $n = 4$, 1.1. To gain added insight, the ^{13}C NMR spectra of the *tert*-cumyl cations were also recorded in FSO_3H–SO_2ClF at −90 °C. The (^+C) ^{13}C NMR shifts correlate in linear fashion with $\cos^2\theta$ ($r = 0.985$), the good data fit clearly indicating a systematic attenuation of charge distribution and implicating the dihedral angle as an important factor in delocalization. In contrast, the rate constant for the fluorenyl analogue fails to correlate with the ^{13}C chemical shift of its cation; it appears to be more reactive than expected on this basis. The results argue for consideration of a decrease in θ for all systems *except fluorenyl* during conversion to the corresponding cation, in an effort to better accommodate the positive charge. Importantly, the linear plot requires that a *proportionate* decrease in θ of similar magnitude be ultimately adopted by **7**, **9**, **10**, and **11**. The enhanced solvolytic rate of the fluorenyl example can then be traced to entropic factors.

The physical basis and limits of homoconjugative interaction, particularly in charged systems, have been a source of fascination to chemists for 20 years.[2] Although precise three-dimensional structural information is still lacking, the extent of interpenetration of the relevant orbitals in such systems (and consequently the resultant overlap integral) is thought to be dependent on internuclear distance and relative spatial orientation.[3]

As an extension of our own involvement with extended homoaromaticity,[3,4] we have presently assessed the relative reactivities of a series of biphenyls bridged at positions 2 and 2′ with hydrocarbon chains composed of one to four methylene units. As denoted in the three-dimensional representations of the limiting extremes indane (**1**) and dibenzo[*a*,*c*]cyclooctadiene (**2**), the principal effect of enlarging the methylene bridge in incremental steps is to twist about the central biphenyl σ bond so as to generate progressively larger angles without greatly perturbing the internuclear distance. Since electronic interaction between the two phenyl rings is presumably dictated in large part by overlap of the π orbitals positioned at C-1 and C-1′, the geometrically imposed twist on this central axis should directly affect the level of interring conjugation. In the



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