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FORMATION OF STABLE SOLVENT-TRAPPED CARBONYL OXIDES FROM THE OZONOLYSIS OF INDOLE DERIVATIVES

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ABSTRACT : Ozonolyses of ethyl indole-2-carboxylate (**1a**) and ethyl 1-methylindole-2-carboxylate (**1b**) in participating solvent, methanol, afforded α-methoxyhydroperoxides **7a** and **7b** in 90 % and 89 % yields, respectively, which are the first isolated solvent-trapped carbonyl oxides from ozonolysis of indole derivatives.

Because of synthetic and biological importance, ozonolyses of a large number of indoles have been conducted and it is generally accepted that the basic Criegee mechanism is operable for the ozonolytic cleavage of the 2,3-double bond of indoles.[1] The intermediacy of the carbonyl oxide for the formation of peroxidic products from ozonolysis of alkenes is the key concept of the Criegee

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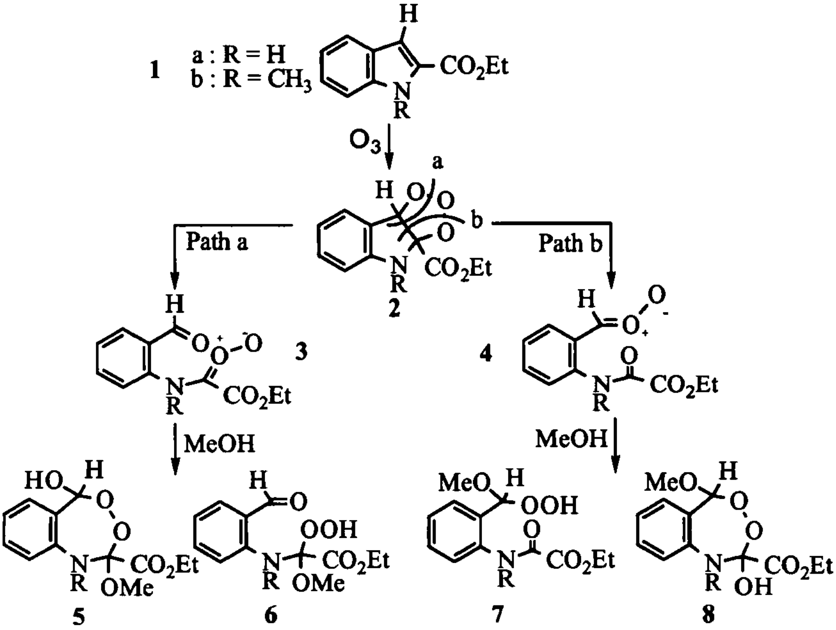
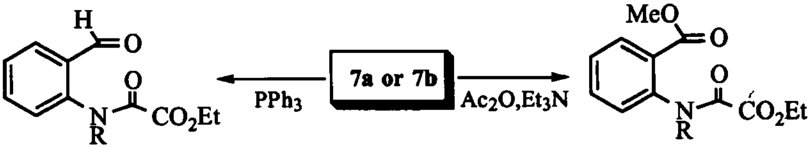
mechanism.[2] However, to the best of our knowledge, no solvent-trapped carbonyl oxide has been isolated from the ozonolysis of indoles to date. Since the formation of stable solvent-derived carbonyl oxides could provide very important information in understanding the mechanism for the ozonolysis of indoles, we wish to report here the first isolation of the solvent-trapped carbonyl oxides, α-methoxyhydroperoxides, from the ozonolysis of indole derivatives **1a** and **1b**.

According to the basic Criegee mechanism, concerted 1,3-dipolar cycloaddition between ozone and the 2,3-double bond of indole will lead to a 1,2,3-trioxolane (PO) **2**. This ozonide **2** may fragment by either of the two possible pathways (path a and b in Scheme 1) providing amide oxide **3** and carbonyl oxide **4**, respectively.[3]



Scheme 1

To determine the fragmentation mode of the PO **2a**, the ozonolysis of ethyl indole-2-carboxylate (**1a**) was carried out in d_4-methanol/CD_2Cl_2 (1:2, v/v) at -78 °C. In the ^1H NMR spectrum of the reaction mixture, the characteristic methoxymethine proton signal for **7a** appeared at 5.74 ppm (s). No aldehyde signal which corresponds to **6a** was observed in the ^1H NMR spectrum. When the same reaction was carried out in methanol/CH_2Cl_2, the methoxy hydroperoxide **7a** was isolated in 90 % yield as a sole product after chromatographic purification. The possibility for the formation of cyclic peroxyhemiacetals **5a** and **8a** was excluded based on the two signals for the amide and ester carbonyls appearing at 154.17 ppm and 160.88 ppm in the ^{13}C NMR spectrum. Treatment of the hydroperoxide **7a** with triphenylphosphine in methylene chloride afforded aldehyde **9a** in 95 % yield. When the hydroperoxide **7a** was treated with acetic anhydride and triethylamine in methylene chloride,[4] the methyl benzoate **10a** was obtained in 92 % yield (scheme 2). These results imply that the PO **2a** fragmented via path b in scheme 1, and the resulting carbonyl oxide **4a** was easily trapped by methanol solvent to give solvent-derived peroxide **7a** which is the first isolated solvent-trapped carbonyl oxide from the ozonolysis of indole derivatives.



9a : 95 % from **7a**
9b : >99 % from **7b**

10a : 92 % from **7a**
10b : 90 % from **7b**

Scheme 2

It is known that *N*-substituted indoles afford no isolable peroxidic ozonolysis products.[1] Thus, after the isolation of the stable solvent-trapped carbonyl oxide **7a** from 2-ethoxycarbonyl substituted indole **1a**, the *N*- methylated

1b was ozonized to examine whether it gives isolable peroxidic products or not. The ozonolysis of **1b** was conducted in methanol/CH_2Cl_2 (1:2, v/v) at -78 °C. After the solvent was removed, amide **7b** was isolated by chromatography on silica gel in 89 % yield. Treatment of **7b** with triphenylphosphine in methylene chloride afforded the aldehyde **9b** as the sole product almost quantitatively, indicating that **7b** is peroxidic (Scheme 2). In addition, when the crude ozonolysis mixture is treated with acetic anhydride and triethyl amine at -78 °C, only the methyl benzoate **10b** was obtained, isolated in 90 % yield after column chromatography. Since **10b** results from trapping of the carbonyl oxide **4b** after trapping by solvent, this implies exclusive fragmentation of **2b** via path b in Scheme 1, to give solvent-derived product from **4b**. In the ^1H NMR spectrum of **7b**, two peroxyacetal methine proton signals at 5.90 ppm and 5.73 ppm are observed in a nearly 1 : 1 ratio. Likewise, two peroxyacetal methine carbons (CH in DEPT) at 104.54 ppm and 103.81 ppm and four carbonyl carbon signals around 160 ppm appeared in the ^{13}C NMR spectra. These observations indicated that **7b** exists as a pair of amide rotamers which are slow to interconvert on the NMR time scale. Consistent with this, the IR spectrum of **7b** exhibited two amide carbonyl absorptions at 1681 and 1666 cm^{-1}. The alternate cyclic peroxide **8b** (which can exist as cis/trans isomers) is excluded by observation of the amide carbonyl signals. The data are best accommodated by the open structure **7b**, as a 1 : 1 mixture of amide rotamers. Unfortunately, attempt to observe the coalesence of the methoxymethine proton signals in elevated temperature was unsuccessful due to the instability of the product. Nevertheless, the isolation of **7b** represents the first solvent-derived peroxidic product obtained from ozonolysis of an *N*-substituted indole derivative.

Even though the carbonyl oxides **4a,b** were formed as the key chloride, produced only the aldehydes **9a** and **9b** in 75 % and 80 % yields, respectively (scheme 2). In the ^{1}H NMR spectra of the reaction mixtures, there was no positive evidence for the formation of normal ozonides formed by intramolecular cyclization of the carbonyl oxide with cognate amide carbonyl fragments in **4**.

In summary, the first solvent-trapped carbonyl oxides were isolated from the ozonolysis of indole derivatives, which strongly suggests that carbonyl oxide is the key intermediate during the ozonolysis of indoles (cyclic enamines).

EXPERIMENTAL

NMR spectra were measured in $CDCl_3$ on a Varian Gemini 300 FT-NMR spectrometer operating at 300 MHz (^{1}H), 75.5 MHz(^{13}C). The chemical shift were relative to internal Me_4Si. IR spectra of neat liquid films were recorded on a MIDAC 101025 FT-IR spectrometer. Chemical analyses were carried out by the Advanced Analysis Center at KIST. Column chromatography was performed on Merk Silica Gel 60 (230~400 mesh). Eluting solvents for all of these chromatographic methods are noted as appropriate-mixed solvents are given in volume-to-volume ratios. Thin-layer chromatography was carried out using glass sheets precoated with silica gel 60F254, supplied by E. Merk. Detection was accomplished by treatment with visualizing agent, phosphomolybdic acid + cerium sulfate solution, followed by warming. Ozone was generated from an Sander Labor-Oznisätor (Artikel Nr.301) using oxygen stream.

General ozonolysis procedure

The indole derivative **1a** or **1b** (mmol) was dissolved in the indicated solvent. O_3 was generated in an oxygen stream and passed through the solution at -78 ℃ until the solution contained excess O_3 as determined by development of a blue coloration. The reaction mixture was purged with N_2 until no residual O_3

remained as indicated by KI/starch paper test of the effluent gas. A drying tube was placed on the flask and the solution was allowed to room temperature. The solvent was removed on the rotatory evaporator and the residue was purified by flash column chromatography on silica gel.

Ozonolysis of ethy indole-2-carboxylate (1a) in MeOH : A solution of **1a** (0.1 M solution) in MeOH and CH_2Cl_2 (1:1, v/v) was ozonized. Purification by chromatography on silica gel afforded α-methoxyhydroperoxide **7a** : R_f = 0.3 (n-hexane : ethyl acetate = 3 : 1 eluent) ; ^{1}H NMR δ 10.52 (bs, 1H), 9.48 (bs, 1H), 8.33 (d, *J* = 8.0 Hz, 1H), 7.38 (t, *J* = 9.6 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.15 (t, *J* = 6.9 Hz, 1H), 5.74 (s, 1H), 4.35 (q, *J* = 7.2 Hz, 2H), 3.69 (s, 3H), 1.39 ppm (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 160.88, 154.17, 135.39, 130.29, 129.04, 124.97, 124.65, 121.67, 108.68, 63.53, 57.05, 13.87 ppm; IR (KBr) 3325, 1765, 1710, 1586, 1292, 1192, 1107 cm^{-1}; Analysis Calc'd for $C_{12}H_{15}NO_6$: C, 53.53; H, 5.62; N, 5.20. Found : C, 53.50; H, 5.62; N, 5.12.

Ozonolysis of ethy indole-2-carboxylate (1a) in CH_2Cl_2 : A solution of **1a** (0.1 M solution) in CH_2Cl_2 was ozonized. Purification by chromatography on silica gel gave aldehyde **9a** in 75 % yield : R_f = 0.3 (n-hexane : ethyl acetate = 8 : 1 eluent) ; ^{1}H NMR δ 12.58 (bs, 1H), 10.02 (s, 1H), 8.80 (d, *J* = 8.3 Hz, 1H), 7.77 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.71 (ddd, *J* = 8.6, 8.3, 1.7 Hz, 1H), 7.37 (dd, *J* = 8.6, 8.3 Hz, 1H), 4.52 (q, *J* = 7.2 Hz, 2H), 1.48 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 194.95, 160.01, 155.28, 138.78, 136.05, 135.99, 124.46, 122.71, 120.24, 63.63, 13.98 ppm. IR (neat) 1744, 1704, 1672, 1590, 1304, 1186 cm^{-1}. Analysis Calc'd for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01; N, 6.33. Found : C, 59.70; H, 5.11; N, 5.97.

Ozonolysis of ethyl 1-methylindole-2-carboxylate (1b) in MeOH : A solution of **1b** (0.1 M solution) in MeOH and CH_2Cl_2 (1:1, v/v) was ozonized. Purification by chromatography on silica gel afforded α-methoxyhydroperoxide **7b** : R_f = 0.4

(n-hexane : ethyl acetate = 3 : 1 eluent); ^{1}H NMR δ 9.74 (bs) and 9.57 (bs) (1H), 7.74 (m) and 7.69 (m) (1H), 7.41 (m, 2H), 7.18 (m, 1H), 5.89 (s) and 5.73 (s) (1H), 4.08 (AB q, *J* = 7.2 Hz) and 3.96 (q, *J* = 7.2 Hz) (2H), 3.69 (s, 3H), 3.34 (s) and 3.31 (s) (3H), 1.11 (t, *J* = 7.2 Hz) and 0.87 (t, *J* = 7.2 Hz) (3H); ^{13}C NMR δ 162.83, 162.25, 161.79, 161.35, 139.22, 138.96, 134.49, 134.12, 130.24, 130.13, 129.31, 129.20, 129.17, 128.86, 128.82, 128.40, 104.54, 103.81, 62.49, 61.76, 57.48, 56.36, 36.80, 13.49 ppm. IR (neat) 3365, 1755, 1681, 1866, 1227 cm^{-1}; Analysis Calc'd for $C_{13}H_{17}NO_6$: C, 55.12; H, 6.05; N, 4.94. Found : C, 55. 30; H, 6.35; N, 4.71.

Ozonolysis of ethyl 1-methylindole-2-carboxylate (1b) in CH_2Cl_2 : A solution of **1b** (0.1 M solution) in CH_2Cl_2 was ozonized. Purification by chromatography on silica gel afforded aldehyde **9b** in 80 % yield : R_f = 0.3 (n-hexane : ethyl acetate = 8 : 1 eluent) ; ^{1}H NMR δ 10.12 (s, 1H), 7.97 (d, *J* = 8.3 Hz, 1H), 7.65 (dd, *J* = 7.6, 8.3 Hz, 1H), 7.56 (dd, *J* = 8.6, 8.3 Hz, 1H), 7.31 (d, *J* = 7.6 Hz, 1H), 3.93 (q, *J* = 7.2 Hz, 2H), 3.34 (s, 3H), 0.94 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 190.95, 159.10, 155.84, 137.87, 135.65, 135.10, 126.64, 122.10, 121.24, 62.34, 37.50, 14.01 ppm.

Reactions of α-alkoxyhydroperoxides 7a and 7b with triphenylphosphine : A solution of **7a** or **7b** (3 mmol) in CH_2Cl_2 (30 mL) was treated with triphenylphosphine (3.3 mmol) at room temperature. After evaporation of the solvent, the residue was purified by column chromatography on silica gel to give aldehyde **9a** and **9b** in 95 % and >99% yields, respectively.

Reactions of α-alkoxyhydroperoxides 7 with acetic anhydride : To a solution of **7a** or **7b** (15 mmol) in CH_2Cl_2 (30 mL) , acetic anhydride (18 mmol) and pyridine (20 mmol) were added via syringe at -78 °C. The reaction mixture was stirred for 1 hr at the same temperature, and then allowed to warm to room temperature. The reaction was quenched by addition of water, and extracted with methylene chloride, dried with anhydrous Na_2SO_4. Evaporation of the solvent and chromatographic purification afforded ester **10a** or **10b** in 92 % and 90 yields, respectively. **10a** : ^{1}H NMR δ 12.58 (bs, 1H), 8.73 (d, *J* =7.4 Hz, 1H), 8.06 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.60 (ddd, *J* = 7.6, 7.4, 1.6 Hz, 1H), 7.21 (dd, *J* =7.8, 7.6 Hz, 1H), 4.43 (q, *J* = 7.2 Hz, 2H), 3.97 (s, 3H), 1.44 ppm (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 168.13, 160.63, 154.75, 139.63, 134.68, 131.01, 123.98, 120.53, 116.30, 63.57, 52.56, 13.99 ppm. IR (neat) 3250, 1736, 1702, 1592, 1534, 1316, 1266 cm^{-1}. **10b** : ^{1}H NMR δ 8.06 (d, *J* = 7.8 Hz, 1H), 7.60 (dd,*J* = 7.6, 7.4 Hz, 1H), 7.45 (dd, *J* =7.8, 7.4 Hz, 1H), 7.34 (d, *J* = 7.6 Hz, 1H) 3.94 (q, *J* = 7.2 Hz, 2H), 3.90 (s, 3H), 3.32 (s, 3H), 0.97 ppm (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 165.25, 161.82, 160.89, 141.14, 133.33, 133.26, 131.77, 129.89, 128.78, 128.35, 128.30, 61.50, 52.55, 36.53, 13.40 ppm.

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