Aerobic Oxidation of 3-Iodomethyl-Δ^3-cephem-4-carboxylate to 3-Formyl-Δ^3-cephem-4-carboxylate through 3-Hydroperoxymethyl-Δ^3-cephem-4-carboxylate

Hideo Tanaka, Ryo Kikuchi, and Sigeru Torii*

Department of Applied Chemistry, Faculty of Engineering, Okayama University, 3-1-1 Tsushima-Naka, Okayama 700

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Aerobic oxidation of *p*-methoxybenzyl 3-iodomethyl-8-oxo-7-phenylacetamido-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (3-iodomethyl-7-phenylacetamido-Δ^3-cephem-4-carboxylate) in *N*-methyl-2-pyrrolidone in the presence of phosphomolybdic acid mainly afforded the corresponding 3-formyl-Δ^3-cephem-4-carboxylate, while similar aerobic oxidation in the presence of potassium iodide gave 3-hydroxymethyl-Δ^3-cephem-4-carboxylate as a major product. 3-Hydroperoxymethyl-Δ^3-cephem-4-carboxylate was isolated as a primary product in the aerobic oxidation, which was subsequently converted to either 3-formyl-Δ^3-cephem-4-carboxylate by dehydration with phosphomolybdic acid or 3-hydroxymethyl-Δ^3-cephem-4-carboxylate by reduction with potassium iodide.

Recently, 3-alkenyl-Δ^3-cephem-4-carboxylic acids, e.g. Cefditoren,[1] Cefprozil,[2] and Cefluprenam,[3] have been intensively investigated as a new cephalosporin antibiotics possessing strong and a broad spectrum of antibacterial activity. 3-Formyl-Δ^3-cephem-4-carboxylate **3** is a potent precursor of the new class of cephalosporin antibiotics since manipulation of the formyl group may provide various C(3)-alkenyl substituents.[4—8] There have been reported a few methods for the preparation of **3**;[5—8] for instance, sequential reactions involving enzymatic hydrolysis (*citrus acetylesterase*) of 3-acetoxymethyl-Δ^3-cephem-4-carboxylates leading to the corresponding 3-hydroxymethyl-Δ^3-cephem-4-carboxylates **4** and subsequent oxidation of **4** with dimethyl sulfoxide/acetic anhydride (DMSO/Ac_2O),[8] chromium trioxide/sulfuric acid (CrO_3/H_2SO_4),[8] or manganese dioxide (MnO_2).[5] These methods, however, involve laborious operations and/or are often accompanied by the undesired migration of the double bond of **3** (Δ^3- to Δ^2-cephem). There still therefore remains great demand on a new synthetic route to **3** to circumvent such drawbacks.

Meanwhile, we have disclosed a straightforward synthesis of 3-chloromethyl-Δ^3-cephem-4-carboxylates **1** from penicillins,[9,10] which has, in turn, directed our attention to a new access to **3** relying on the transformation of chloromethyl group of **1** to the 3-formyl moiety. Recently, we and another group have independently reported new synthetic routes to 3-formyl-Δ^3-cephem-4-carboxylates through aerobic oxidation of 3-halomethyl-Δ^3-cephem-4-carboxylates. Thus, Ikeda et al. envisioned an aerobic oxidation of 3-chloromethyl-Δ^3-cephem-4-carboxylate **1** in the presence of sodium iodide in a methanol/dichloromethane (5/1) mixed solvent affording 3-formyl-Δ^3-cephem-4-carboxylate dimethyl acetal (40—40.5%), which was submitted to deacetalization leading to 3-formyl-Δ^3-cephem-4-carboxylates **3**.[11] In a preliminary report, we disclosed an aerobic oxidation of 3-iodomethyl-Δ^3-cephem-4-carboxylates **2**, easily derived from **1**, in the presence of rhodium trichloride trihydrate/aluminum ($RhCl_3 \cdot 3H_2O$/Al), vanadyl acetylacetonate ($VO(acac)_2$), or vanadyl sulfate ($VOSO_4$) in *N*,*N*-dimethylformamide (DMF).[12] These procedures are, however, still unsatisfactory because of the low yields of **3** and/or use of large excess amounts of expensive reagents. In our continuing investigation, we found that aerobic oxidation of 3-iodomethyl-Δ^3-cephem-4-carboxylate **2** (R^2 = *p*-methoxybenzyl) afforded 3-hydroperoxymethyl-Δ^3-cephem-4-carboxylate **5** as a primary product which could be converted into 3-formyl-Δ^3-cephem-4-carboxylate **3** and/or 3-hydroxymethyl-Δ^3-cephem-4-carboxylate **4** depending on the choice of additives. Herein, we describe that (1) aerobic oxidation of 3-iodomethyl-Δ^3-cephem-4-carboxylate **2** in the presence of phosphomolybdic acid ($P_2O_5 \cdot 24MoO_3 \cdot xH_2O$, 22 wt%) in *N*-methyl-2-pyrrolidone (NMP) afforded the 3-formyl-Δ^3-cephem-4-carboxylate **3** in moderate yield (54%), (2) a similar oxidation of **2** in the presence of potassium iodide (5 molar amounts) in 10 vol% aqueous NMP gave the 3-hydroxymethyl-Δ^3-cephem-4-carboxylate **4** (52%), and (3) 3-hydroperoxymethyl-Δ^3-cephem-4-carboxylate **5** was formed as a primary product in the aerobic oxidation and subsequently converted to 3-formyl-Δ^3-cephem-4-carboxylate **3** and 3-hydroxymethyl-Δ^3-cephem-4-carboxylate **4**, respectively.

Experimental

Materials. 3-Iodomethyl-Δ^3-cephem-4-carboxylate **2** (R^2 = *p*-methoxybenzyl) was prepared by treatment of the corresponding 3-chloromethyl-Δ^3-cephem-4-carboxylate **1** with NaI (1.05 molar amounts) in acetone under reflux (93%).[12] *N*-Methyl-2-pyrrolidone (NMP) was distilled over potassium hydride under nitrogen

and stored under nitrogen. Water was deionized and subsequently distilled before use. All other chemicals and solvents were used as supplied without further purification.

Instrumentation. NMR spectra were determined with a Varian VXR-200 (200 MHz for proton and 50 MHz for carbon-13) or Varian VXR-500 (500 MHz for proton). The ^{1}H NMR signals in chloroform-*d* are expressed in ppm downfield from internal tetramethylsilane (0 ppm), and those in DMF-d_7 are expressed in ppm based on the formyl proton observed in DMF-d_7 as a reference (8.05 ppm). The ^{13}C NMR signals are expressed in ppm using chloroform-*d* as a reference (77 ppm). IR spectra were obtained with a JASCO FT-IR-5000 spectrometer in wavenumber (cm^{-1}). Mass spectra were recorded with Hitachi M-80 double focusing mass spectrometer. High performance liquid chromatography (HPLC) was executed with Hitachi HPLC instrument equipped with L-6000 LC pump, L-4000 UV detector, and 833A integrator.

Aerobic Oxidation of 3-Iodomethyl-Δ^3-cephem-4-carboxylate 2 in the Presence of Phosphomolybdic Acid. A mixture of 3-iodomethyl-Δ^3-cephem-4-carboxylate **2** (R^2 = *p*-methoxybenzyl, 576 mg, 1 mmol) and phosphomolybdic acid (134 mg) in NMP (10 ml) was stirred under bubbling oxygen at 35—37 °C. After most of **2** was consumed (4 h), an aliquot of the reaction mixture was analyzed by HPLC,[13] showing the presence of 3-formyl-Δ^3-cephem-4-carboxylate **3** (54%) and 3-hydroxymethyl-Δ^3-cephem-4-carboxylate **4** (6%). The reaction mixture was diluted with ethyl acetate and the solution was washed with water, 5% $Na_2S_2O_3$, and brine. The organic layer was separated and dried over $MgSO_4$. After evaporation of solvents, the residue was chromatographed using ODS silica gel (CH_3CN/H_2O: 55/45—60/40) to give 3-formyl-Δ^3-cephem-4-carboxylate **3**[12] (220 mg, 47%): IR (KBr) 3266, 3036, 2962, 1796, 1725, 1665, 1611, 1518 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ = 3.23 (d, J = 18 Hz, 1H), 3.65 (ABq, J = 16 Hz, 2H), 3.81 (s, 3H), 3.97 (d, J = 18 Hz, 1H), 4.98 (d, J = 5 Hz, 1H), 5.28 (ABq, J = 11 Hz, 2H), 5.94 (dd, J = 5, 9 Hz, 1H), 6.14 (d, J = 9 Hz, 1H), 6.90 (m, 2H), 7.22—7.45 (m, 7H), 9.78 (s, 1H); ^{1}H NMR (500 MHz, DMF-d_7) 3.54 (d, J = 18 Hz, 1H), 3.70 (ABq, J = 14 Hz, 2H), 3.86 (s, 3H), 4.01 (d, J = 18 Hz, 1H), 5.39 (d, J = 5 Hz, 1H), 5.41 (ABq, J = 12 Hz, 2H), 6.10 (dd, J = 5, 9 Hz, 1H), 7.03 (m, 2H), 7.26—7.50 (m, 7H), 9.14 (d, J = 9 Hz, 1H), 9.81 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 22.2, 43.1, 55.2, 58.9, 59.9, 69.2, 114.1, 123.7, 125.9, 127.7, 129.2, 129.3, 130.9, 133.5, 160.1, 165.2, 171.1, 187.1; FDMS *m/z* 466 (M^+).

Aerobic Oxidation of 3-Iodomethyl-Δ^3-cephem-4-carboxylate 2 in the Presence of Potassium Iodide. A mixture of 3-iodomethyl-Δ^3-cephem-4-carboxylate **2** (R^2 = *p*-methoxybenzyl, 578 mg, 1 mmol) and potassium iodide (826 mg, 5 molar amounts) in 10% aqueous NMP (10 ml) was stirred under an oxygen atomsphere (1 atm) at 35—37 °C. After most of **2** was consumed (2.5 h), an aliquot of the reaction mixture was analyzed by HPLC,[13] showing the presence of 3-hydroxymethyl-Δ^3-cephem-4-carboxylate **4** (52%) and 3-formyl-Δ^3-cephem-4-carboxylate **3** (5%). The reaction mixture was diluted with ethyl acetate and the solution was washed with dilute brine, 5% $Na_2S_2O_3$, and brine. The organic layer was separated and dried over $MgSO_4$. After evaporation of solvents, the residue was chromatographed using ODS silica gel (CH_3CN/H_2O: 55/45) to give 3-hydroxymethyl-Δ^3-cephem-4-carboxylate **4**[14] (203 mg, 43%): IR (KBr) 3360, 1780, 1720, 1655, 1517, 1249, 1176, 1104, 1029 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 3.53 (s, 2H), 3.64 (ABq, J = 16 Hz, 2H), 3.81 (s, 3H), 3.92 (d, J = 13 Hz, 1H), 4.44 (d, J = 13 Hz, 1H), 4.88 (d, J = 5 Hz, 1H), 5.20 (ABq, J = 12 Hz, 2H), 5.83 (dd, J = 5, 9 Hz, 1H), 6.07 (d, J = 9 Hz, 1H), 6.89 (m, 2H), 7.24—7.40 (m, 7H); ^{1}H NMR (500 MHz, DMF-d_7), 3.70 (ABq, J = 14 Hz, 2H), 3.71 (s, 2H), 3.84 (s, 3H), 4.41 (d, J = 6 Hz, 2H), 5.18 (d, J = 5 Hz, 1H), 5.21 (d, J = 12 Hz, 1H), 5.24 (t, J = 6 Hz, 1H), 5.29 (d, J = 12 Hz, 1H), 5.85 (dd, J = 5, 8 Hz, 1H), 7.00 (m, 2H), 7.25—7.45 (m, 7H), 9.01 (d, J = 8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 27.2, 43.2, 55.2, 57.2, 59.1, 61.7, 68.2, 113.9, 124.7, 126.5, 127.6, 129.0, 129.3, 130.6, 131.8, 133.7, 159.9, 162.3, 165.0, 171.3.

***p*-Methoxybenzyl 3-Hydroperoxymethyl-8-oxo-7-phenylacetamido-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (5).** A mixture of 3-iodomethyl-Δ^3-cephem-4-carboxylate **2** (R^2 = *p*-methoxybenzyl, 58 mg, 0.1 mmol) in NMP (1 ml) was stirred at 33—37 °C for 3 h under oxygen atmosphere. Immediately after the reaction, the mixture was diluted with 1 ml of acetonitrile/water (1 : 1) and submitted to reverse-phase chromatography using a column packed with ODS silica gel (CH_3CN/H_2O: 1/1) to give 3-hydroperoxymethyl-Δ^3-cephem-4-carboxylate **5** (15 mg, 32%): IR (KBr) 3358, 2928, 2854, 1782, 1720, 1660, 1613, 1516, 1455, 1390, 1366, 1342, 1304, 1249, 1177, 1104, 1066, 1033, 827, 733, 697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 3.46 (d, J = 18 Hz, 1H), 3.61 (d, J = 18 Hz, 1H), 3.64 (ABq, J = 16 Hz, 2H), 3.80 (s, 3H), 4.71 (d, J = 15 Hz, 1H), 4.94 (d, J = 5 Hz, 1H), 4.95 (d, J = 15 Hz, 1H), 5.18 (s, 2H), 5.81 (dd, J = 5, 9 Hz, 1H), 6.10 (d, J = 9 Hz, 1H), 6.88 (m, 2H), 7.25—7.40 (m, 7H), 8.35 (br s, 1H); ^{1}H NMR (500 MHz, DMF-d_7) 3.70 (ABq, J = 14 Hz, 2H), 3.76 (ABq, J = 18 Hz, 2H), 3.84 (s, 3H), 4.73 (d, J = 14 Hz, 1H), 4.95 (d, J = 14 Hz, 1H), 5.21 (d, J = 5 Hz, 1H), 5.26 (ABq, J = 12 Hz, 2H), 5.89 (dd, J = 5, 9 Hz, 1H), 7.00 (m, 2H), 7.25—7.50 (m, 7H), 9.03 (d, J = 9 Hz, 1H), 12.12 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 14.2, 21.1, 26.1, 43.2, 55.3, 57.5, 59.1, 60.4, 68.1, 75.0, 113.9, 125.4, 126.6, 127.7, 128.2, 129.1, 129.4, 130.6, 130.7, 133.6, 159.9, 161.6, 164.7, 171.5. Anal. Calcd for $C_{24}H_{24}N_2O_7S$: C, 59.49; H, 4.99; N, 5.78%. Found: C, 58.80; H, 5.31; N, 5.69%.[15,16]

Results and Discussion

A mixture of 3-iodomethyl-Δ^3-cephem-4-carboxylate **2** (R^2 = *p*-methoxybenzyl) in NMP[17] was stirred for 3 h in the presence of phosphomolybdic acid (22 wt% based on **2**) at 35—37 °C under an oxygen atmosphere (1 atm), affording 3-formyl-Δ^3-cephem-4-carboxylate **3** (54%) together with a small amount of 3-hydroxymethyl-Δ^3-cephem-4-carboxylate **4** (2%) (Entry 1 in Table 1). The presence of ca. 20 wt% of phosphomolybdic acid is indispensable for the predominant formation of aldehyde **3**. Thus, aerobic oxidation of **2** with a reduced amount of phosphomolybdic acid (8 wt%, Entry 2 in Table 1) resulted in decrease of **3** (44%) and increase of **4**

Table 1. Aerobic Oxidation of **2**

Entry	Additive (molar amount)	Time / h	Yield/%[a] **3**	Yield/%[a] **4**
1	$P_2O_5 \cdot 24MoO_3 \cdot xH_2O$ (22)[b]	3	54	2
2	$P_2O_5 \cdot 24MoO_3 \cdot xH_2O$ (8)[b]	3	44	7
3	—	7	26	20
4	$P_2O_5 \cdot 24MoO_3 \cdot xH_2O$ (42)[b]	3	53	Trace
5	$P_2O_5 \cdot 24MoO_3 \cdot xH_2O$ (92)[b]	3	48	Trace
6	KI (1)	2	8	41[d]
7	KI (5), H_2O (10)[c]	3	5	52

a) Determined by HPLC. b) wt%. c) vol%. d) 20% of **2** was recovered.

(7%), and in the absence of phosphomolybdic acid, an almost 1 to 1 mixture of **3** and **4** was obtained (Entry 3). On the other hand, the presence of a larger amount of phosphomolybdic acid (42 and 92 wt%) almost completely eliminated the formation of **4**, but the yield of **3** decreased to 48% (Entries 4 and 5). In contrast, the aerobic oxidation of the iodide **2** in the presence of potassium iodide (1 molar amount) afforded the alcohol **4** as a major product (Entry 6). Furthermore, addition of 10 vol% of water together with potassium iodide (5 molar amounts) resulted in increase of the yield of **4** up to 52% (Entry 7). The significant effects of phosphomolybdic acid and potassium iodide can be reasonably explained by assuming that the aerobic oxidation proceeds via 3-hydroperoxymethyl-Δ^3-cephem-4-carboxylate **5** which is, in turn, converted to 3-formyl-Δ^3-cephem-4-carboxylate **3** or to 3-hydroxymethyl-Δ^3-cephem-4-carboxylate **4** depending on the choice of the additives (Scheme 1).

The formation of the intermediary hydroperoxide **5** in the aerobic oxidation of **2** leading to **3** and **4** can be supported by the analyses of the reaction course by HPLC and ^{1}H NMR. Thus, the time-course of the aerobic oxidation of **2** without any additives (Fig. 1) showed that the hydroperoxide **5** was accumulated as decrease of the substrate **2**, and the amount of **5** reached a maximum when most of **2** was consumed (2—2.5 h). The hydroperoxide **5** was then gradually diminished while the amounts of the aldehyde **3** and the alcohol **4** were increased. The ^{1}H NMR of the reaction mixture of the aerobic oxidation of **2** in 1 vol% aqueous DMF-d_7 also showed the formation of the intermediary hydroperoxide **5** (Fig. 2). Thus, the characteristic signals of **5** at 5.88(dd), 5.27(ABq), 5.21(d), and 4.85(ABq) ppm were observed together with those assigned to **2** and **3**.

Isolation and identification of the hydroperoxide **5** were performed as follows. The aerobic oxidation of **2** was carried out without any additives at 35—37 °C for 3 h under oxygen atmosphere, and the reaction mixture was immediately submitted to a reverse-phase chromatography affording **5** (32%). The ^{1}H NMR and IR spectra are well in accordance with the proposed structure **5**.[15] Ikeda et al. proposed a mechanism involving 3-iodosylmethyl-Δ^3-cephem-4-carboxylate **6** and its rearranged species, i.e. hypoiodite ester **7**, as plausible intermediates in the aerobic oxidation of 3-chloromethyl-Δ^3-cephem-4-carboxylate **2** in the presence of sodium iodide (Scheme 2).[11] It seems not the case of the present aerobic oxidation since the elemental analysis of **5** undoubtedly ruled out such iodine-containing derivatives.[16]

All of the observations mentioned above indicate that the hydroperoxide **5** must be an intermediate in the aerobic oxidation of **2** to **3** and **4**. Next, the role of the additives, i.e. phosphomolybdic acid and potassium iodide, was investigated by the following experiments: The aerobic oxidation of **2** was carried out without additives until most of **2** was consumed, and then phosphomolybdic acid (21 wt%) was added. As shown in Fig. 3, the amount of aldehyde **3** was nonlinearly increased immediately after the addition of phosphomolybdic acid, indicating that dehydration of **5** is accelerated by phosphomolybdic acid. On the other hand, the reduction of **5** into the alcohol **4** took place preferentially when potassium iodide (2 molar amounts) was added (Fig. 4). Similarly, triphenylphosphine (2 molar amounts)

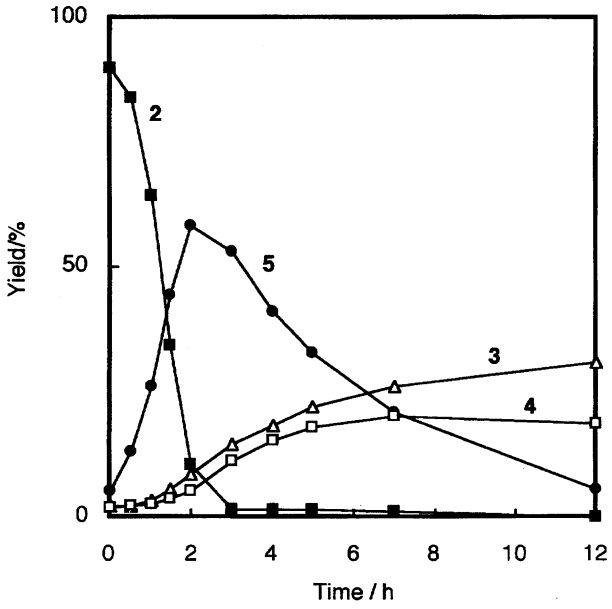
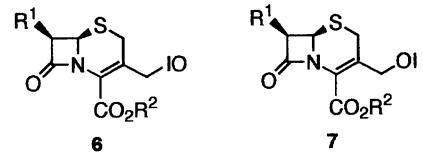
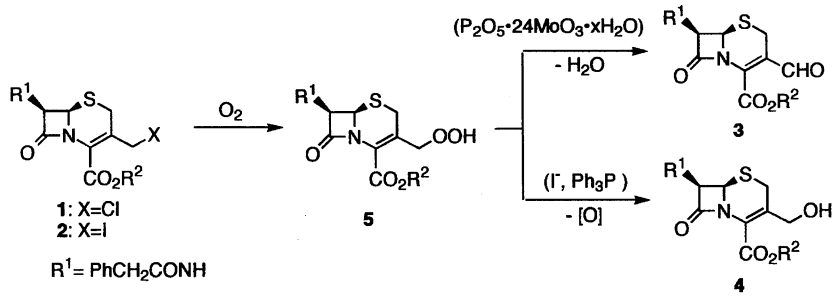


Fig. 1. The time-course of the aerobic oxidation of 3-iodomethyl-Δ^3-cephem-4-carboxylate **2**.



Scheme 2. Iodine-containing intermediates.[11]



Scheme 1. Aerobic oxidation of 3-iodomethyl-Δ^3-cephem-4-carboxylate **2**.

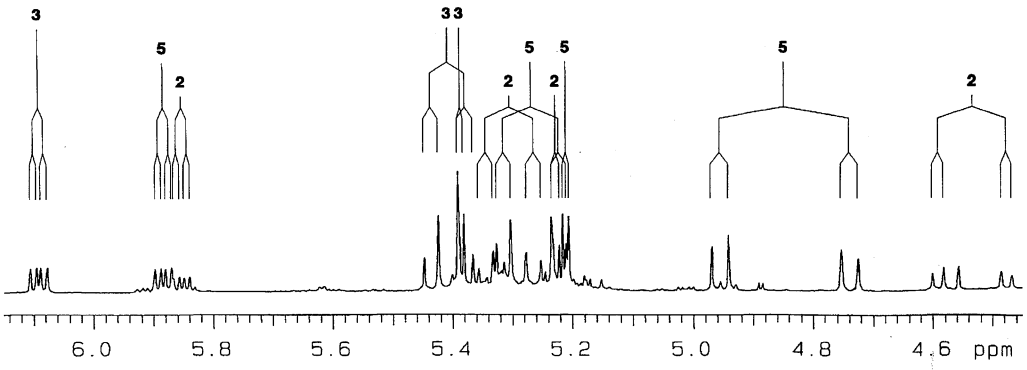


Fig. 2. The ^{1}H NMR spectra (500 MHz) of the reaction mixture on the course of aerobic oxidation of 3-iodomethyl-Δ^3-cephem-4-carboxylate **2** in 1 vol% aqueous DMF-d_7 (30 min).

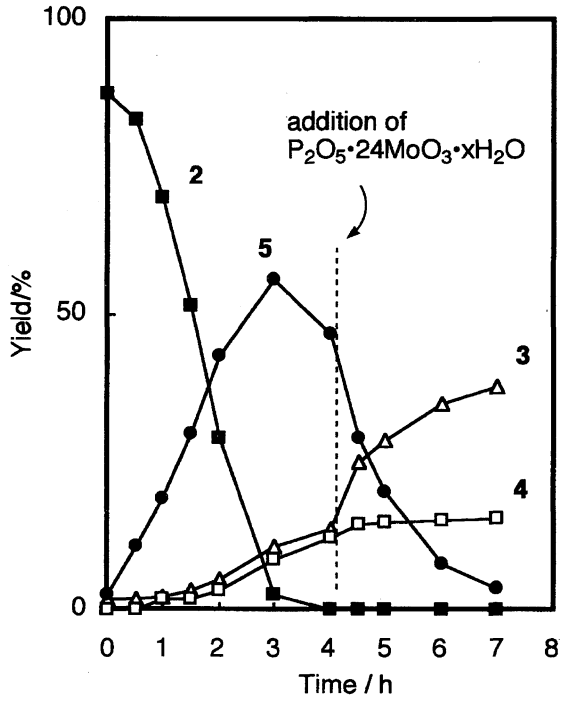


Fig. 3. The time-course of the aerobic oxidation of 3-iodomethyl-Δ^3-cephem-4-carboxylate **2**. P_2O_5·24MoO_3·xH_2O (21 wt%) was added to the reaction mixture after most of **2** was consumed.

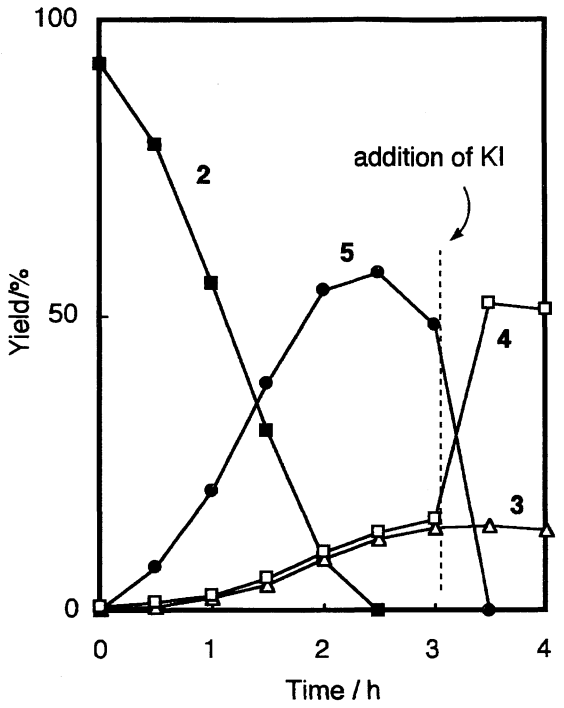
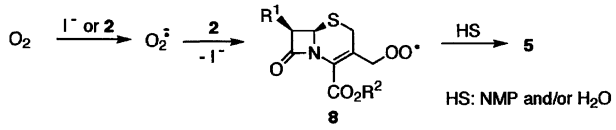


Fig. 4. The time-course of the aerobic oxidation of 3-iodomethyl-Δ^3-cephem-4-carboxylate **2**. KI (2 molar amounts) was added to the reaction mixture after most of **2** was consumed.

also effected the reduction of **5**. Thus, the selective transformation of the hydroperoxide **5** to the aldehyde **3** or alcohol **4** was realized by proper choice of the additives.

Although the mechanism of the formation of 3-hydroperoxymethyl-Δ^3-cephem-4-carboxylate **5** in the aerobic oxidation of 3-iodomethyl-Δ^3-cephem-4-carboxylate **2** is not clear at present, nucleophilic substitution of **2** with superoxide anion followed by hydrogen abstraction would be a plausible pathway leading to **5** (Scheme 3).[18] Valentine et al. reported that the reaction of primary iodides with superoxide gave the corresponding alcohols as major products together with small amounts of aldehydes.[19] Actually, treatment of **2** with potassium superoxide (2 molar amounts) in the presence of 18-crown-6 (3 molar amounts)in NMP under argon atmosphere gave the alcohol **4** (21%) and the hydroperoxide



Scheme 3. A plausible mechanism of formation of 3-hydroperoxymethyl-Δ^3-cephem-4-carboxylate **5**.

5 (18%) together with a small amount of the aldehyde **3** (2%). The formation of the superoxide in the aerobic media can be explained by assuming one-electron reduction of molecular oxygen with the iodide **2** or a small amount of iodide ion liberated from **2**.[20]

Conclusion

Aerobic oxidation of 3-iodomethyl-Δ^3-cephem-4-carboxylate **2** in *N*-methyl-2-pyrrolidone afforded the 3-formyl-Δ^3-cephem-4-carboxylate **3** in moderate yield (54%) in the presence of phosphomolybdic acid (22 wt%). On the other hand, a similar oxidation of **2** in the presence of potassium iodide (5 molar amounts) in 10 vol% aqueous NMP gave the 3-hydroxymethyl-Δ^3-cephem-4-carboxylate **4** (52%). The ^{1}H NMR spectra (DMF-d_7) and HPLC analysis of the reaction mixture showed that the 3-hydroperoxymethyl-Δ^3-cephem-4-carboxylate **5** would be formed as a primary product in the aerobic oxidation, and subsequently converted to **3** and **4** by dehydration and reduction, respectively.

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13) The condition of HPLC analysis was as follows: column YMC-Pack AM-312 ODS (6 mmϕ × 150 mm), mobile phase CH_3CN/H_2O 65 : 35, flow rate 1 ml min^{-1}, detection UV 254 nm. External standard method was employed for determination of products and substrates.

14) H. Tanaka, T. Yamaguchi, M. Taniguchi, Y. Kameyama, M. Sasaoka, T. Shiroi, and S. Torii, *Chem. Express*, **6**, 435 (1991).

15) Unfortunately, the molecular ion peak of the hydroperoxide **5** was not clearly observed in EI-MS, FDMS, and SIMS, probably because of lability of **5** under the MS conditions. FDMS *m/z* (rel intensity) 485 (7), 484 (M^+; 8), 483 (3), 482 (16), 466 (100).

16) The elemental analysis of **5** varied in the range of 58.57—58.80% for carbon, 5.23—5.31% for hydrogen, and 5.69—6.11% for nitrogen, probably because of lability of **5**. But these data support the structure **5** rather than iodine-containing structures, i.e. an iodosyl derivative **6** and a hypoiodite ester **7**; Calcd for **6** and **7** ($C_{24}H_{23}N_2O_6S$): C, 48.49; H, 3.90; N, 4.71%.

17) NMP is the best choice among the solvents investigated so far. The aerobic oxidation of **2** was similarly performed in DMF and *N*,*N*-dimethylacetamide affording 48 and 43% yields of **3**, respectively, but not in dimethyl sulfoxide (DMSO), diglyme, and acetylacetone (yields of **3** <8%).

18) The other plausible pathways to **5**, e.g. oxygenation of the carbon radical species derived from **2** and oxidation of **2** with in situ generated hydrogen peroxide are not necessary to be ruled out at present, but the following facts are notable; (1) The aerobic oxidation of **2** in NMP in the presence of radical scavengers, e.g. hydroquinone, afforded **5** in 55% yield. (2) The reaction of **2** with 30% hydrogen peroxide (2 molar amounts) in NMP under argon atmosphere (2 h) gave no appreciable amounts of **3**, **4**, and **5**.

19) J. S. Filippo, Jr., C. -I. Chern, and J. S. Valentine, *J. Org. Chem.*, **40**, 1678 (1975).

20) Similar transformation from molecular oxygen into superoxide with iodide was proposed: M. H. Boyer and J. B. Ramsey, *J. Am. Chem. Soc.*, **75**, 3802 (1953).