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## Chemoselective Aerobic Oxidation of Penicillin and Cephalosporin Derivatives into Sulfoxides

Hideo Tanaka, Ryo Kikuchi, Sigeru Torii \*

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

**Abstract:** Aerobic oxidation of penicillin and cephalosporin derivatives in the presence of cobalt(III) acetylacetonate and an aldehyde under oxygen atmosphere took place in a chemoselective manner to afford the corresponding sulfoxides, exclusively.

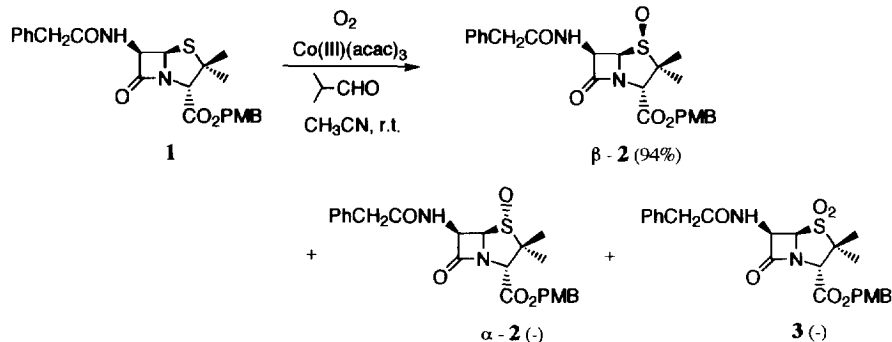
### INTRODUCTION

Sulfoxide is an important functionality in organic synthesis and various kinds of oxidants have been developed for the oxidation of sulfide into the sulfoxide.<sup>1,2)</sup> In the chemical modifications of penicillin and cephalosporin derivatives into useful  $\beta$ -lactam antibiotics, chemoselective oxidation of the sulfide moiety into sulfoxide has often been employed as an essential step.<sup>2)</sup> Recently, aerobic oxidation catalyzed by transition metal complexes in the presence of a reducing agent, *e.g.*, aldehydes, has been intensively investigated for various oxidative transformations of organic molecules,<sup>3)</sup> *e.g.*, epoxidation of olefins,<sup>3a)</sup> Baeyer-Villiger Oxidation,<sup>3a)</sup> and carbon-carbon double bond fission.<sup>3d)</sup> Aerobic oxidation of sulfides into the sulfoxides under similar conditions has also been focused on, especially in the synthesis of optically active sulfoxides.<sup>3b-c)</sup> The aerobic oxidation of sulfides investigated so far has, however, been limited to that of simple sulfides and chemoselectivity of the aerobic oxidation of multifunctionalized sulfides, such as penicillin and cephalosporin derivatives, has not been elucidated. Herein, we describe aerobic oxidation of penicillin and cephalosporin derivatives in the presence of cobalt(III) acetylacetonate and an aldehyde, in which, chemoselective oxidation of the sulfide moieties can be achieved to afford the corresponding sulfoxides, exclusively (Scheme 1).

### RESULTS AND DISCUSSION

At first, the aerobic oxidation of penicillin G *p*-methoxybenzyl ester **1** was carried out in the presence of cobalt(III) acetylacetonate (0.1 equivalent) and isobutyraldehyde (3.5 equivalents) in acetonitrile or dichloroethane at room temperature under oxygen atmosphere. After most of **1** was consumed (3 h), usual workup gave the corresponding  $\beta$ -sulfoxide  $\beta$ -**2** in 94-95% yield (Scheme 1). Notably, the aerobic oxidation of **1** to **2** proceeded in a chemo- and stereo-selective manner; indeed, no appreciable amount of  $\alpha$ -sulfoxide  $\alpha$ -**2**, sulfone **3**, and other oxidation products were obtained.

The presence of both cobalt(III) acetylacetonate and isobutyraldehyde is indispensable for the aerobic oxidation of **1** since the lack of either the cobalt(III) complex or the aldehyde resulted in recovery of most of the substrate **1**. It is normally expected that the oxidation of **1** would be promoted by *in situ* generated oxidants under the aerobic conditions. In this connection, it should be noted that the coexistence of three components,

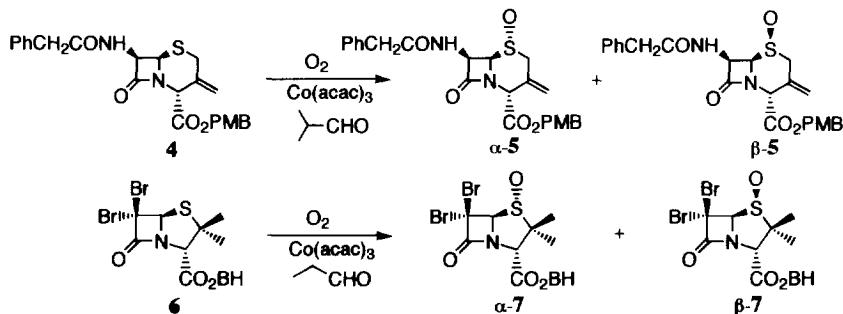


Scheme 1. Aerobic Oxidation of **1** Catalyzed by Co(III) Complex (PMB = *p*-methoxybenzyl)

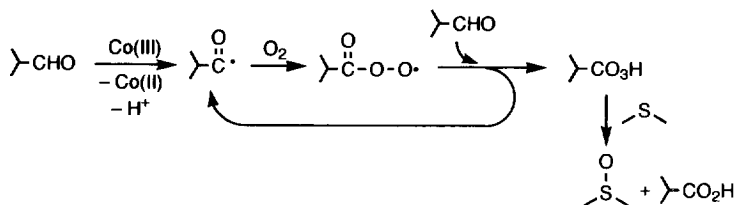
*i.e.*, the substrate **1**, the cobalt(III) catalyst, and the aldehyde, is essential for the oxidation of the sulfide moiety of **1**; thus, a mixture of cobalt(III) acetylacetonate and isobutyraldehyde was stirred for 10 h under oxygen atmosphere without the sulfide **1**, then, into the mixture was added **1**, and the stirring was continued for additional 5 h under argon atmosphere, resulting in almost complete recovery of the substrate **1**. This fact indicates that the *in situ* generated oxidants would not be accumulated in the aerobic oxidation media; indeed, any oxidants in the pretreated solution prior to the addition of **1** were not detected by potassium iodide/starch paper.

Next, the cobalt(III)-catalyzed aerobic oxidation was applied to the transformation of 3-exomethylenecepham **4** and 6,6-dibromopenicillin **6** into the corresponding sulfoxides **5** and **7**, key-intermediates for the synthesis of useful  $\beta$ -lactam antibiotics<sup>2i)</sup> and  $\beta$ -lactamase inhibitors.<sup>2c)</sup> The aerobic oxidation of 3-exomethylenecepham **4** catalyzed by cobalt(III) acetylacetonate (0.1 equivalent) with isobutyraldehyde (3.5 equivalents) proceeded smoothly to give the sulfoxide **5** in 72% yield ( $\alpha/\beta = 32:68$ ), in which, neither overoxidation of **5** into the corresponding sulfone nor oxidation of 3-exomethylene moiety was observed. On the other hand, a mixture of 6,6-dibromopenicillin **6**, cobalt(III) acetylacetonate (0.1 equivalent), and isobutyraldehyde (3.5 or 7 equivalents) in acetonitrile was stirred under oxygen atmosphere for 13 h, resulting in a low conversion of **6** into **7** (ca. 10%). The oxidation of **6** was successfully achieved by modification of the procedure; thus, propionaldehyde (5 equivalents) was added portionwise during the course of the reaction (22 h) affording the sulfoxide **7** in 81% yield ( $\alpha/\beta = 91:9$ ).<sup>4)</sup>

The oxidation of the sulfide **4** with *m*-chloroperbenzoic acid (*m*-CPBA, 1.2 equivalents) in acetonitrile gave the sulfoxides **5** in 92% yield in an  $\alpha/\beta$  ratio of 15:85 together with a small amount of the corresponding



PMB = *p*-methoxybenzyl; BH = diphenylmethyl



Scheme 2. A Plausible Mechanism in Co(III)-Catalyzed Aerobic Oxidation of Sulfides.

sulfone (4%). Notably, the ratio of  $\alpha$ -sulfoxide **5** and  $\beta$ -sulfoxide **5** is comparable to that of the aerobic oxidation of **4**. The  $\alpha/\beta$  ratio of **7** (91:9) in the aerobic oxidation of **6** is also agreed to that reported for the oxidation of **6** with *m*-CPBA ( $\alpha/\beta = 10:1$ ).<sup>2c</sup> From these results, peracid, which would be derived from aldehyde and molecular oxygen in the presence of cobalt(III) catalyst, is likely the main active species in the cobalt(III)-catalyzed aerobic oxidation of sulfides. A plausible mechanism of the formation of peracid is illustrated in Scheme 2: thus, oxidation of the aldehyde with cobalt(III) complex gives the corresponding acyl radical which affords the acylperoxy radical through capture of molecular oxygen. The subsequent hydrogen abstraction of acylperoxy radical from another aldehyde molecule leading to the peracid accompanied with regeneration of the acyl radical (a radical chain process).<sup>5</sup> The accumulation of the oxidant, *i.e.*, peracid, was, however, not observed in the aerobic media (*vide supra*). The contradict results can be reasonably explained by assuming that, in the absence of sulfides, the *in situ* generated peracid would be decomposed gradually presumably by reaction with the excess amount of aldehyde and/or by degradation catalyzed by the resulting cobalt(II) species.<sup>5</sup> This assumption is also well in accordance with the fact that the aerobic oxidation of 6,6-dibromopenicillin **6** into **7** can be achieved only by portionwise addition of aldehyde (*vide supra*), in which *in situ* generated peracid would be allowed to react with less reactive sulfide as well as aldehyde.

The cobalt(III) complex is the proper choice for the aerobic oxidation of sulfides since cobalt(II) catalysts, such as cobalt(II) acetylacetonate dihydrate and cobalt(II) chloride, could not efficiently promote the oxidation of the sulfides. The cobalt(III)-initiated radical chain process leading to peracid shown in Scheme 2 would work only with cobalt(III) catalysts but not with the cobalt(II) catalysts. For instance, the aerobic oxidation of the sulfide **1** with cobalt(II) acetylacetonate dihydrate and isobutyraldehyde (3 h) resulted in recovery of most of the starting material **1** together with a trace amount of sulfoxide **2** (less than 1% yield). In the aerobic oxidation of **4** using cobalt(II) chloride as a catalyst, only 41% yield of the sulfoxide **5** was obtained even after prolonged reaction time (22 h, 54% recovery of **4**) and, notably, the  $\alpha/\beta$  ratio of the sulfoxide **5** was inverted to 68:32. This fact led us to consider that a different type reaction occurs in the cobalt(II)-catalyzed aerobic oxidation of sulfides. In this context, we investigated manganese(III)-catalyzed oxidation of sulfide **4** in which, oxomanganese complex was expected to work as an oxygen donor.<sup>6</sup> Thus, the oxidation of **4** with a manganese(III)-Schiff base complex (Mn(III)(salen)•OAc, 0.1 equivalent) and iodosylbenzene (1.2 equivalents) was carried out in acetonitrile for 11 h at room temperature to give the  $\alpha$ -sulfoxide **5** as a major product (41%;  $\alpha/\beta = 73:27$ ) together with recovery of **4** (34%). The proximity of  $\alpha/\beta$  selectivity and efficiency of the cobalt(II)- and manganese(III)-catalyzed oxidations of **4** to **5** suggests that oxocobalt species would play a significant role in the cobalt(II)-catalyzed oxidation of sulfides.<sup>7</sup>

## CONCLUSION

Chemoselective oxidation of penicillin and cephalosporin derivatives **1**, **4**, and **6** into the corresponding sulfoxides was achieved in an aerobic oxidation catalyzed by cobalt(III) acetylacetonate in the presence of isobutyraldehyde or propionaldehyde. The portionwise addition of aldehyde is effective for the oxidation of sulfide **6** reluctant to be oxidized. Cobalt(III) acetylacetonate is known to catalyze aerobic oxidation of olefins to

epoxides<sup>3e</sup>) and cyclic ethers to lactones<sup>8</sup>) in the presence of a reducing agent. Nevertheless, the overoxidation of the sulfoxides was not observed and the other functionalities such as carbon-carbon double bond, amide moieties, and benzylic methylene, survived the aerobic oxidation conditions. On the other hand, cobalt(II)-catalyzed oxidation of 3-exomethylenecepham **4** proceeded less efficiently to give the sulfoxide **5** (41%) with the inverted selectivity of  $\alpha$ - and  $\beta$ -sulfoxide. The differences between the cobalt(III)- and cobalt(II)-catalyzed oxidations of the sulfide **4** suggest that two different oxidants, *i.e.*, peracid and oxocobalt species, would be formed, respectively.

## EXPERIMENTAL

**Materials.** Penicillin G *p*-methoxybenzyl ester **1**, 3-exomethylenecepham *p*-methoxybenzyl ester **4**, and 6,6-dibromopenicillin diphenylmethyl ester **6** were gifts from Otsuka Chemical Co. Ltd. and used without further purification. Isobutyraldehyde and propionaldehyde were purified by distillation before use. Acetonitrile was distilled over phosphorus pentoxide under nitrogen. 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). The <sup>1</sup>H NMR signals in chloroform-*d* are expressed in ppm downfield from internal tetramethylsilane (0 ppm). The <sup>13</sup>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<sup>-1</sup>). Mass spectra were recorded with HITACHI M-80 double focusing mass spectrometer. Melting point was obtained with YANACO MP-J3 Micro Melting Point Apparatus.

**Oxidation of Sulfides 1 and 4.** A mixture of **1** (113 mg, 0.25 mmol) or **4** (113 mg, 0.25 mmol), cobalt(III) acetylacetonate (8.5 mg, 0.1 equivalent), and isobutyraldehyde (79  $\mu$ l, 3.5 equivalents) in acetonitrile (2 ml) was stirred under oxygen atmosphere (balloon) at room temperature. After most of the substrate was consumed (3 h), the reaction mixture was diluted with ethyl acetate and the solution was washed with water, 5% Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>, and brine. The organic layer was separated and dried over MgSO<sub>4</sub>. After evaporation of solvents, the residue was chromatographed (SiO<sub>2</sub>, dichloroethane/ethyl acetate: 4/1) to give the corresponding sulfoxides  $\beta$ -**2** (94%) or **5** ( $\beta$ -**5** 49%,  $\alpha$ -**5** 23%). The stereochemistry of the sulfoxides **2** and **5** was determined by comparison of the spectral data and the melting point with those reported in literatures and/or those of the authentic samples prepared by the reported procedures.<sup>9,10</sup>

***p*-Methoxybenzyl (4S)-3,3-Dimethyl-7-oxo-6-phenylacetamido-4-thia-1-azabicyclo-[3.2.0]heptane-2-carboxylate 4-oxide ( $\beta$ -2):**<sup>9</sup> IR (KBr) 3360, 2961, 1794, 1746, 1687, 1515, 1252, 1207, 1036 cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$  = 1.00 (s, 3H), 1.60 (s, 3H), 3.56 (s, 2H), 3.80 (s, 3H), 4.60 (s, 1H), 4.94 (d, *J* = 4.6 Hz, 1H), 5.15 (ABq, *J* = 11.7 Hz, 2H), 6.01 (dd, *J* = 4.6, 10.3 Hz, 1H), 6.89 (m, 2H), 7.13 (d, *J* = 10.3 Hz, 1H), 7.20-7.40 (m, 7H); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>)  $\delta$  = 18.2, 19.3, 43.2, 55.1, 56.2, 66.0, 67.6, 75.2, 76.6, 113.9, 126.6, 127.3, 128.8, 129.1, 130.6, 133.7, 159.9, 167.6, 170.5, 173.5; mp 150 °C (lit.<sup>9</sup>) 149 °C).

***p*-Methoxybenzyl (5S)-3-Exomethylene-8-oxo-7-phenylacetamido-5-thia-1-azabicyclo-[4.2.0]octane-2-carboxylate 5-oxide ( $\beta$ -5):**<sup>10</sup> IR (KBr) 3433, 1775, 1740, 1649, 1518, 1256, 1175, 1026 cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$  = 3.48 (d, *J* = 13.9 Hz, 1H), 3.59 (s, 2H), 3.66 (d, *J* = 13.9 Hz, 1H), 3.81 (s, 3H), 4.80 (d, *J* = 4.6 Hz, 1H), 5.10 (ABq, *J* = 11.8 Hz, 2H), 5.16 (s, 1H), 5.37 (d, *J* = 1.5 Hz, 1H), 5.67 (s, 1H), 5.92 (dd, *J* = 4.6, 10.3 Hz, 1H), 6.89 (m, 2H), 6.93 (d, *J* = 10.3 Hz, 1H), 7.20-7.40 (m, 7H); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>)  $\delta$  = 43.5, 49.5, 55.3, 55.7, 59.6, 66.8, 67.9, 114.1, 123.8, 126.3, 126.5, 127.4, 128.9, 129.3, 130.2, 133.6, 160.0, 165.1, 167.5, 171.0; FDMS *m/z* 468 (M<sup>+</sup>).

***p*-Methoxybenzyl (5R)-3-Exomethylene-8-oxo-7-phenylacetamido-5-thia-1-azabicyclo-[4.2.0]octane-2-carboxylate 5-oxide ( $\alpha$ -5):** IR (KBr) 3440, 1781, 1741, 1665, 1516, 1250, 1175, 1031 cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$  = 3.52 (d, *J* = 12.7 Hz, 1H), 3.64 (s, 2H), 3.81 (s, 3H), 3.97 (d, *J* = 12.7 Hz, 1H), 4.67 (d, *J* = 4.3 Hz, 1H), 5.02 (s, 1H), 5.14 (s, 2H), 5.20 (dd, *J* = 4.3, 7.8 Hz, 1H), 5.39 (s,

2H), 6.32 (d,  $J = 7.8$  Hz, 1H), 6.89 (m, 2H), 7.20-7.42 (m, 7H);  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta = 42.7, 54.1, 55.2, 55.6, 60.7, 67.9, 76.7, 114.0, 122.2, 126.5, 127.5, 129.0, 129.4, 129.8, 130.3, 133.6, 159.9, 163.3, 167.1, 172.0$ ; FDMS  $m/z$  468 ( $\text{M}^+$ ). Anal. Calcd. for  $\text{C}_{24}\text{H}_{24}\text{N}_2\text{O}_6\text{S}$ : C, 61.53; H, 5.16; N, 5.98. Found: C, 61.48; H, 5.23; N, 5.80.

**Oxidation of Sulfides 6.** Into a mixture of **6** (131 mg, 0.25 mmol), cobalt(III) acetylacetonate (8.5 mg, 0.1 equivalent) in acetonitrile (4 ml) was added propionaldehyde (88  $\mu\text{l}$ , 5 equivalents) over a period of 12 h under oxygen atmosphere (balloon) at 34-36 °C. After most of the substrate was consumed (22 h), the reaction mixture was diluted with ethyl acetate and the solution was washed with water, 5%  $\text{Na}_2\text{S}_2\text{O}_3$ , and brine. The organic layer was separated and dried over  $\text{MgSO}_4$ . After evaporation of solvents, the residue was chromatographed ( $\text{SiO}_2$ , benzene-benzene/ethyl acetate: 4/1) to give the  $\alpha$ - and  $\beta$ -sulfoxides **7** (74 and 7%, respectively). The stereochemistry of the sulfoxides **7** was determined by comparison of the spectral data with those reported in literatures and/or those of the authentic samples prepared by the reported procedures.<sup>2c)</sup>

**Diphenylmethyl (4R)-6,6-Dibromo-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate 4-oxide ( $\alpha$ -7):**<sup>2c)</sup> IR (KBr) 1805, 1752, 1297, 1216, 1181, 1071  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta = 1.21$  (s, 3H), 1.56 (s, 3H), 4.67 (s, 1H), 5.31 (s, 1H), 6.94 (s, 1H), 7.30-7.40 (m, 10H);  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta = 16.4, 24.5, 47.6, 66.6, 72.3, 79.5, 92.5, 126.9, 127.3, 128.3, 128.5, 128.6, 138.4, 138.6, 162.1, 165.2$ .

**Diphenylmethyl (4S)-6,6-Dibromo-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate 4-oxide ( $\beta$ -7):**<sup>2c)</sup> IR (KBr) 1809, 1752, 1209, 1182, 1067, 700  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta = 0.95$  (s, 3H), 1.68 (s, 3H), 4.82 (s, 1H), 5.21 (s, 1H), 6.97 (s, 1H), 7.30-7.40 (m, 10H);  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta = 17.9, 19.7, 44.1, 65.7, 74.9, 79.1, 83.7, 126.8, 127.5, 128.3, 128.6, 128.7, 138.6, 138.9, 163.7, 166.1$ .

**Oxidation of Sulfide 4 Catalyzed by Cobalt(II) Chloride.** A mixture of **4** (112 mg, 0.25 mmol), cobalt(II) chloride (3.4 mg, 0.1 equivalent), and isobutyraldehyde (79  $\mu\text{l}$ , 3.5 equivalents) in acetonitrile (4 ml) was stirred for 22 h under oxygen atmosphere (balloon) at room temperature. The reaction mixture was diluted with ethyl acetate and the solution was washed with water, 5%  $\text{Na}_2\text{S}_2\text{O}_3$ , and brine. The organic layer was separated and dried over  $\text{MgSO}_4$ . After evaporation of solvents, the residue was chromatographed ( $\text{SiO}_2$ , dichloroethane/ethyl acetate: 4/1) to give  $\alpha$ -**5** (28%) and  $\beta$ -**5** (13%) together with the starting material (54% recovery).

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