Disinfection By-Products of *para*-Hydroxybenzoate Esters (Parabens): Synthesis and Mass Spectrometric Study

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A simple and efficient procedure for the chlorination of *para*-hydroxybenzoate esters (parabens) with sulfuryl chloride is described. Fourteen monochlorinated or dichlorinated parabens were synthesized and their mass spectrometric characteristics were determined. This work enabled the definitive identification and quantification of the chlorinated parabens in environmental samples.

Key words —— disinfection by-product, paraben, chlorination, standard material, gas chromatography-mass spectrometry

INTRODUCTION

Hydroxybenzoate esters (parabens) are a group of chemicals widely used as preservatives in personal care products such as sunscreen creams, bath gels, shampoos, toothpastes, etc. due to their relatively low toxicity profile and a long history of safe use.[1] In general, many personal care products are used daily in various human activities; therefore, they are continuously released in the aquatic environment through domestic wastewater. Some parabens have been identified as an emerging class of potential pollutants for the aquatic environment. For example, methyl, ethyl, propyl, and butyl parabens have been detected in sewage treatment plant (STP) influents at a level of μg/l.[2,3] The methyl, propyl, and butyl parabens were also found in the STP effluents at the level of μg/l.[3]

Drinking water treatment primarily relies upon adsorptive and oxidative processes to remove or transform organic pollutants. However, the addition of common disinfectants can result in the reaction and transformation of these compounds.[4] The possibility that the chemicals used in personal care products might reach potable water sources has fostered studies aiming toward studying the formation of undesirable by-products during water treatments such as chemical disinfection.[5,6] Certain disinfection by-products are toxic species that might pose a potential risk to the human health.[7] Particularly, compounds containing phenolic hydroxyl groups in their structures demonstrate favorable chlorination kinetics;[8–10] consequently, the disinfection by-products may occur when personal care products containing parabens are mixed with chlorinated water.

In recently reported disinfection by-products of parabens, the analysis of several raw wastewater samples showed the existence of dichlorinated parabens.[11] Although the identification and quantification of chlorinated parabens in such water samples requires the standard materials to be authentic, only a few authentic chlorinated parabens are currently commercially available. In this study, we describe an aromatic chlorination process using sulfuryl chloride as a reagent and determine the mass spectrometric characteristics of the authentic chlorinated parabens.

Many of the available methods for the direct chlorination of aromatic systems involve the use of potentially hazardous elemental chlorine or expensive transition metal based catalysts.[12] The handling of chlorine gas is cumbersome due to its hazardous nature, while special equipment and care is required for the transfer of this material on a large scale. The application of sulfuryl chloride in chlorinating electron-rich aromatic compounds is one of the simple methods.[13,14] These reactions are generally high-yielding when the functionalities are compatible with this reagent.

MATERIALS AND METHODS

Chemicals —— Methyl-, ethyl-, *n*-butylparaben, and sulfuryl chloride were purchased from Wako Pure Chemical Industries, Osaka, Japan. The chemicals *n*-propyl-, *i*-propyl-, *i*-butyl- and benzylparaben were purchased from Tokyo Chemical Industry, Tokyo, Japan. All other chemicals and solvents used were of analytical grade or HPLC grade.

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Synthesis —— The typical experimental procedure and the spectral data obtained in this study are as follows: A paraben (1 mmol) dissolved in a solvent (2 ml) was added to sulfuryl chloride dropwise and capped, and the mixture was heated at 80°C. After cooling, volatile solvents were removed under a reduced pressure, and the crude product was taken in ethyl acetate and washed with water, 5% sodium bicarbonate solution, and brine and dried over anhydrous sodium sulphate. The solvents were evaporated under a reduced pressure and placed in an evacuated desiccator in the presence of phosphorus pentoxide for a day to yield the chlorinated parabens. After recrystallization from ether/hexane, resulting products were characterized by a melting point (mp), NMR spectroscopy, and high-resolution fast atom bombardment tandem mass spectrometry (FAB-MS). Mp were recorded on a BY-1 micro melting point apparatus (Yazawa Scientific, Tokyo, Japan) without correction. ^{1}H NMR spectra were recorded in *d*-chloroform on a JEOL ECA 500 spectrometer (JEOL, Tokyo, Japan) operating at 500 MHz. Chemical shifts for spectra taken in *d*-chloroform are recorded in δ (ppm) values relative to tetramethylsilane δ 0.00. FAB-MS spectra were recorded on a JMS-700 instrument (JEOL, Tokyo, Japan). The ion source was operated at 10 kV full accelerating voltage with a mass resolution of 3000 (10% valley). The FAB gun was operated with Xe gas at an emission current of 5 mA and at an acceleration voltage of 6 kV. Samples were dissolved in acetone and mixed with 3-nitrobenzyl alcohol as a matrix. Calibration of the mass scale was achieved by using a polyethylene glycol (PEG 200) in the positive-ion mode.

Analytical Methods —— The standard and sample extracts were analyzed by employing GC-MS (GC: HP 6890 Series; Hewlett-Packard, Palo Alto, CA, U.S.A.; MS: HP 5972A Series mass-selective detector; Hewlett-Packard) on a HP-5 fused-silica capillary column (internal diameter, 30 m × 0.32 mm; film thickness, 0.25 μm; J&W Scientific, Folsom, CA, U.S.A.). The column temperature was initially maintained at 80°C for 1 min; it was then programmed to approach 180°C at a rate of 4°C/min, and subsequently, 280°C at a rate of 10°C/min with a final hold time of 5 min. Helium was used as a carrier gas with a flow rate of 1.0 ml/min, and the column head pressure was maintained at 8.0 psi. The injector temperature was maintained at 250°C and the injection volume was 1.0 μl in the splitless mode. The electron multiplier voltage for MS was 1988 V, and the interface temperature was maintained at 280°C. The mass spectra were obtained by electron impact ionization at a voltage of 70 eV and scanned within a range of *m/z* 50 to 550 atomic mass units at a rate of 1.5 scans per second, and the ion source temperature was maintained at 250°C. The authentic samples in ethyl acetate were trimethylsilylated with BSTFA before the GC-MS analysis.

The partition coefficients for octanol and water were calculated using the LogKow program.[15)]

RESULTS AND DISCUSSION

Synthesis of Chlorinated Parabens

First, optimize a suitable chlorinating system of isopropylparaben. The reaction is slow at room temperature, and it is necessary to maintain an elevated temperature. Solvent screening is performed using ethyl acetate to identify the best solvent for this reaction (data not shown). We continue to expand the scope of this methodology; a number of parabens are also subjected to the chlorination reaction under heating in ethyl acetate, and the results of this process are summarized in Table 1. The desired monochloroparabens **8**–**14** are isolated in excellent yields (89–99%). Similarly, the dichlorination of parabens with excess sulfuryl chloride results in the clean formation of dichloroparabens **15**–**21** in high yields (97–99%). In addition, to the best of our knowledge, parabens possessing long carbon chain esters (compounds **11**–**14**, **18**–**20**) have not been commercially available.[16)] The selected physical and spectral data of them are shown below.

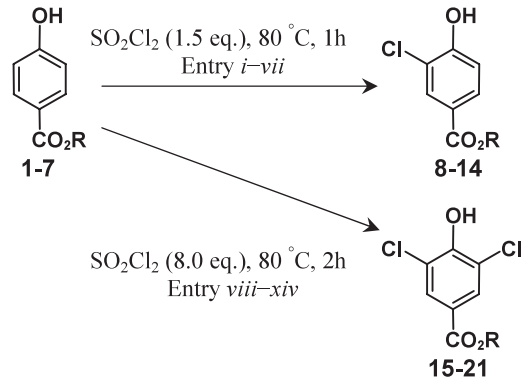
Isopropyl 3-chloro-4-hydroxybenzoate (***11***): mp 86–88°C. ^{1}H NMR δ 1.35 (*d*, 6 H, J = 6.3 Hz, -CH_3× 2), 5.22 (*sept*, 1 H, J = 6.3 Hz, -CH), 5.91 (*s*, 1 H, -OH), 7.04 (*d*, 1 H, J = 8.6 Hz, Ar-H), 7.88 (*dd*, 1 H, J = 1.7 and 8.6 Hz, Ar-H), 8.02 (*d*, 1 H, J = 1.7 Hz, Ar-H). HR FAB+MS *m/z* 215.0442 $[M+H]^+$ (calcd. for 215.0476; $C_{10}H_{12}O_3{}^{35}Cl$), 217.0421 (calcd. for 217.0446; $C_{10}H_{12}O_3{}^{37}Cl$).

Butyl 3-chloro-4-hydroxybenzoate (***12***): mp 45–48°C. ^{1}H NMR δ 0.97 (*t*, 3 H, J = 7.5 Hz, -CH_3), 1.46 (*sext*, 2 H, J = 7.4 Hz, -CH_2), 1.73 (*quint*, 2 H, J = 6.9 Hz, -CH_2), 4.29 (*t*, 2 H, J = 6.9 Hz, -CH_2), 5.92 (*s*, 1 H, -OH), 7.05 (*d*, 1 H, J = 8.6 Hz, Ar-H), 7.89 (*dd*, 1 H, J = 1.7 and 8.6 Hz, Ar-H), 8.03 (*d*, 1 H, J = 1.7 Hz, Ar-H). HR FAB+MS *m/z* 229.0633 $[M+H]^+$ (calcd. for 229.0632; $C_{11}H_{14}O_3{}^{35}Cl$), 231.0555 (calcd. for 231.0602; $C_{11}H_{14}O_3{}^{37}Cl$).

Isobutyl 3-chloro-4-hydroxybenzoate (***13***): mp 53–55°C. ^{1}H NMR δ 1.01 (*d*, 6 H, *J* = 6.3 Hz, -CH_3× 2), 2.06 (*sept*, 1 H, *J* = 6.3 Hz, -CH), 4.07 (*d*, 2 H, *J* = 6.9 Hz, -CH_2), 5.92 (*s*, 1 H, -OH), 7.05 (*d*, 1 H, *J* = 8.6 Hz, Ar-H), 7.89 (*dd*, 1 H, *J* = 1.7 and 8.6 Hz, Ar-H), 8.03 (*d*, 1 H, *J* = 1.7 Hz, Ar-H). HR FAB+MS *m/z* 229.0620 $[M+H]^+$ (calcd. for 229.0632; $C_{11}H_{14}O_3{}^{35}Cl$), 231.0572 (calcd. for 231.0602; $C_{11}H_{14}O_3{}^{37}Cl$).

Benzyl 3-chloro-4-hydroxybenzoate (***14***): mp 82–84°C. ^{1}H NMR δ 5.33 (*s*, 2 H, -CH_2), 5.93 (*s*, 1 H, -OH), 7.05 (*d*, 1 H, *J* = 8.6 Hz, Ar-H), 7.33–7.46 (*m*, 5 H, At-H), 7.92 (*dd*, 1 H, *J* = 2.3 and 8.6 Hz, Ar-H), 8.06 (*d*, 1 H, *J* = 2.3 Hz, Ar-H). HR FAB+MS *m/z* 263.0426 $[M+H]^+$ (calcd. for 263.0476; $C_{14}H_{12}O_3{}^{35}Cl$), 265.0391 (calcd. for

Table 1. Results of the Optimization Process Toward the Monochlorination or Dichlorination of Parabens



Entry	R	Reactant	Product	Yield, %
i	Me	**1**	**8**	89
ii	Et	**2**	**9**	92
iii	Pr	**3**	**10**	97
iv	*iso*Pr	**4**	**11**	99
v	Bu	**5**	**12**	95
vi	*iso*Bu	**6**	**13**	97
vii	Bn	**7**	**14**	99
viii	Me	**1**	**15**	97
ix	Et	**2**	**16**	96
x	Pr	**3**	**17**	98
xi	*iso*Pr	**4**	**18**	96
xii	Bu	**5**	**19**	99
xiii	*iso*Bu	**6**	**20**	99
xiv	Bn	**7**	**21**	99

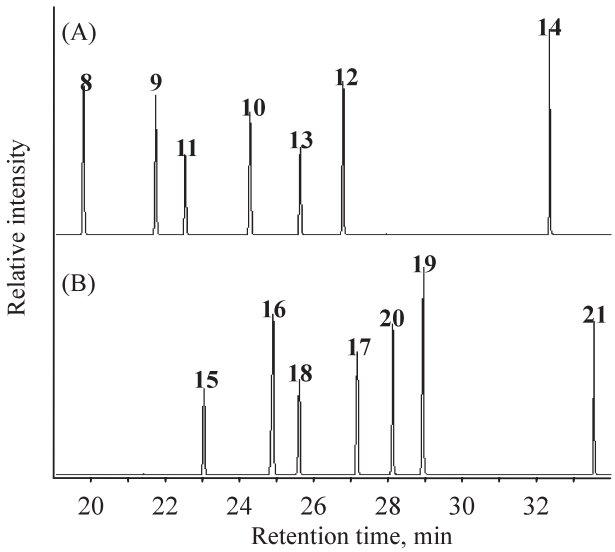


Fig. 1. GC-MS Total Ion Chromatograms of Monochlorinated Parabens (A) and Dichlorinated Parabens (B)

Table 2. Mass Spectral Data Using EI as Ionization Mode and Log *p* Values of the Chlorinated Parabens

No.	MS characterization (relative abundance, %), Underline denotes molecular ion peak	Log *p*
8	119 (100), 243 (92), 245 (32), 258 (21), 260 (7)	2.64
9	73 (100), 257 (94), 259 (34), 272 (23), 274 (8)	3.13
10	73 (100), 271 (80), 229 (36), 273 (30), 286 (19), 288 (7)	3.62
11	73 (100), 271 (77), 229 (50), 273 (29), 286 (23), 288 (9)	3.55
12	73 (100), 229 (71), 285 (66), 287 (24), 300 (17), 302 (7)	4.11
13	73 (100), 229 (89), 285 (40), 287 (15), 300 (11), 302 (4)	4.04
14	91 (100), 227 (36), 229 (13), 319 (6), 334 (4), 336 (1)	4.35
15	277 (100), 279 (67), 292 (16), 294 (11)	3.29
16	291 (100), 293 (67), 306 (16), 308 (11)	3.78
17	305 (100), 73 (92), 307 (69), 263 (19), 320 (13), 322 (9)	4.27
18	305 (100), 73 (98), 307 (68), 263 (39), 320 (16), 322 (11)	4.19
19	73 (100), 319 (71), 321 (48), 263 (42), 334 (9), 336 (6)	4.76
20	73 (100), 319 (93), 321 (63), 263 (34), 334 (11), 336 (7)	4.69
21	91 (100), 353 (15), 261 (15), 365 (11), 263 (10), 368 (4), 370 (3)	4.99

265.0446; $C_{14}H_{12}O_3{}^{37}Cl$).

Isopropyl 3,5-dichloro-4-hydroxybenzoate (***18***): mp 97–98°C. ^{1}H NMR δ 1.35 (*d*, 6 H, J = 6.3 Hz, -CH_3 × 2), 5.21 (*sept*, 1 H, J = 6.3 Hz, -CH), 6.21 (*s*, 1 H, -OH), 7.95 (*s*, 2 H, Ar-H). HR FAB+MS *m/z* 249.0108 $[M+H]^+$ (calcd. for 249.0086; $C_{10}H_{11}O_3{}^{35}Cl_2$), 251.0097 (calcd for 251.0056; $C_{10}H_{11}O_3{}^{35}Cl_1{}^{37}Cl_1$), 253.0061 (calcd. for 253.0026; $C_{10}H_{11}O_3{}^{37}Cl_2$).

Butyl 3,5-dichloro-4-hydroxybenzoate (***19***): mp 79–81°C. ^{1}H NMR δ 0.97 (*t*, 3 H, J = 7.4 Hz, -CH_3), 1.45 (*sext*, 2 H, J = 7.5 Hz, -CH_2), 1.74 (*quint*, 2 H, J = 7.5 Hz, -CH_2), 4.30 (*t*, 2 H, J = 6.3 Hz, -CH_2), 6.22 (*s*, 1 H, -OH), 7.96 (*s*, 2 H, Ar-H). HR FAB+MS *m/z* 263.0255 $[M+H]^+$ (calcd. for 263.0243; $C_{11}H_{13}O_3{}^{35}Cl_2$), 265.0226 (calcd. for 265.0213; $C_{11}H_{13}O_3{}^{35}Cl_1{}^{37}Cl_1$), 267.0216 (calcd. for 267.0183; $C_{11}H_{13}O_3{}^{37}Cl_2$).

Isobutyl 3,5-dichloro-4-hydroxybenzoate (***20***): mp 93–96°C. ^{1}H NMR δ 1.01 (*d*, 6 H, J = 6.9 Hz, -CH_3 × 2), 2.07 (*sept*, 1 H, J = 6.6 Hz, -CH), 4.08 (*d*, 2 H, J = 6.3 Hz, -CH_2), 6.22 (*s*, 1 H, -OH), 7.96 (*s*, 2 H, Ar-H). HR FAB+MS *m/z* 263.0224 $[M+H]^+$ (calcd. for 263.0243; $C_{11}H_{13}O_3{}^{35}Cl_2$), 265.0226 (calcd. for 265.0213; $C_{11}H_{13}O_3{}^{35}Cl_1{}^{37}Cl_1$), 267.0184 (calcd. for 267.0183; $C_{11}H_{13}O_3{}^{37}Cl_2$).

GC-EI-MS Characteristics of Chlorinated Parabens

The total ion chromatogram of the authentic compounds of the chlorinated parabens is shown in Fig. 1, and the *m/z* ratios for the mean ions in the MS spectra of the authentic compounds and the values of their logarithmic partition coefficient log p are listed in Table 2. The observed peaks apparently became longer due to a longer retention time, except for that of dichloromethylparaben (**15**), with an increase in the log p values of the chlorinated parabens, indicating that elution order depends on the degree of polarity for chlorinated parabens. The MS spectra of the authentic compounds presented the typical isotopic pattern of molecular ions corresponding to monochlorinated and dichlorinated compounds. The chlorinated parabens reacted with BSTFA to produce the corresponding trimethylsilyl derivatives. The base peaks in their spectra corresponded to the loss of trimethylsilyl cations, and therefore they appeared at *m/z* 73. However, the mass spectra for chlorinated propyl and isopropyl parabens (**17**, **18**) were dominated by the mass clusters at [M-15] *m/z* units due to the loss of a methyl moiety in derivatives, and those for compounds **14** and **21** were dominated by a benzyl cation at *m/z* 91.

In conclusion, we have successfully prepared several important chlorinated parabens in a simple and efficient reaction to obtain excellent yields. Furthermore, no side reaction such as the elimination of ester has been observed during the chlorination; therefore, sufficiently pure products (> 97%) have been obtained in high yields. The GC-EI-MS characteristics are expected to support environmental chemical studies such as the aqueous environmental fate and the kinetics of chlorinated parabens. The results of these investigations will be presented in due course.

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