2-(5-Oxo-2-(phenylmethylene)-2*H*-oxazol-4-yl)-5,5-dimethyl-4-thiazolidinecarboxylic Acid. To a solution of 4.3 g (0.02 mol) of 6-aminopenicillanic acid dissolved in 100 mL of water by the addition of 4 g of $NaHCO_3$ was added at 5 °C dropwise 4.7 mL (0.02 mol) of α-bromophenylacetyl chloride in 30 mL of acetone. The mixture was stirred for 1 h and acidified to pH 2 with concentrated hydrochloric acid. A yellow solid was isolated and recrystallized from methanol–ether to yield 2.4 g (38%) of a mixed hydrobromide, hydrochloride salt. This was converted to the base by dissolving in sodium bicarbonate solution at pH 8.4 and adjusting to pH 5 with acetic acid to yield 1.5 g: mp 127 °C dec; IR (KBr) 3400, 2500–3000, 1780, 1740, 1655, 1230, 695 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.36 (s, 3 H, Me), 1.64 (s, 3 H, Me), 4.16 (s, 1 H, C-4H), 5.88 (s, 1 H, C-2H), 6.78 (s, 1 H, C-9H), 7.2–7.7 (m, 3 H, C-4″H, C-5″H, C-6″H), 7.7–8.1 (m, 2 H, C-1″H, C-6H); ^{13}C NMR ($CDCl_3$) δ 172.4 (C-6), 161.9 (C-5′), 156.6 (C-4′), 152.1 (C-2), 131.9 (C-1″), 131.0 (C-2″,C-6″), 130.1 (C-4″), 127.0 (C-3″, C-5″), 114.8 (C-9), 73.0 (C-4), 59.9 (C-2, C-5), 27.9 and 27.2 (C-7, C-8); mass spectrum, *m/z* (relative intensity) 333 (80), 332 M^+ (20), 289 (78), 263 (30), 257 (30, 136 (100); UV λ_{max}^{MeOH} 242 (ε7074), 359 (21494), 377 (18948). Anal. Calcd for $C_{16}H_{16}N_2O_4S \cdot H_2O$: C, 55.14; H, 4.63; N, 8.04. Found: C, 54.73; H, 4.75; N, 7.97; KF (H_2O) 3.81.

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Registry No. 3, 102921-27-7; 6-aminopenicillanic acid, 551-16-6; α-bromophenylacetyl chloride, 19078-72-9.

Diagnosing Consecutive Reactions of Hypochlorite: pH and Oxidative Decarboxylation/Halogenation

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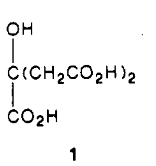
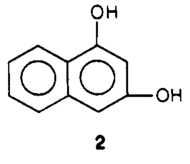
In addition to the classic "haloform" reaction of methyl ketones,[1] trihalomethanes result readily from hypohalous acid/hypohalite reactions of certain carboxylic acids[2] and amino acids,[3] as well as from activated β-diketones, meta-dihydroxylated aromatics, and quinones.[4-6] With some of these substrates, halogenation is but one component of a complex series of competitive and/or consecutive reactions.

A case in point is the reaction of citric acid (1), which over 100 years ago was discovered to yield CO_2, pentachloroacetone, and $CHCl_3$ on treatment with aqueous chlorine.[2a] On treatment with NaOCl/HOCl solutions, compound 1 gives a higher yield of $CHCl_3$ at pH 7 than at pH 9.[2b] In contrast, production of $CHCl_3$ from 1,3-dihydroxynaphthalene (2) has been found to be more facile at pH 11 than at pH 7.[6b] Therefore, it was important to discover that substantial increases in pH may occur during the course of hypochlorite reactions with either 1 or 2, reflecting production of multichlorinated products.



$HOC(CH_2CO_2H)_2CO_2H$

1



2

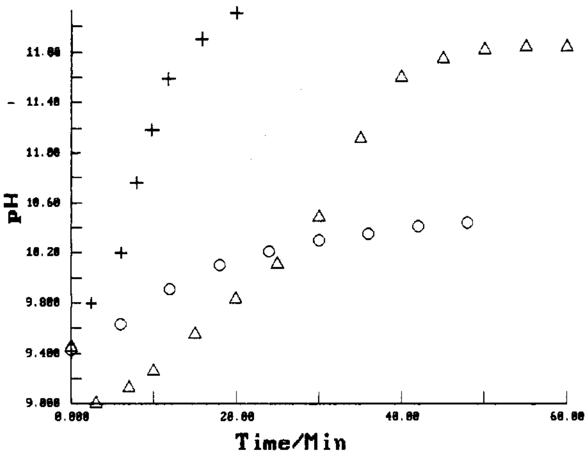


Figure 1. pH profiles of chloroform precursors with 10-fold excess of sodium hypochlorite at initial concentration = 0.68–0.74 M: + = acetone; ○ = citric acid; △ = 2-hydroxy-2-methylpropanoic acid.

Scheme I

$$R_2C(OH)CO_2H \xrightarrow{NaOCl} R_2C(O) + CO_2$$

1, R = CH_2CO_2H
3, R = CH_3
4, R = Ph
5, R = CH_2CH_3

For hypochlorite-induced oxidation of aromatic hydrocarbons, provision must be made to keep the pH from dropping during reactions, due to the acidic nature of products, CO_2, and benzenecarboxylic acids.[7] However, when the aromatic substrate 2 was subjected to reaction with hypochlorite at pH 9, a rapid increase (to pH >11.5 in less than 5 s) was observed. This occurred in spite of the fact that both CO_2 and phthalic acid were produced in significant yields.

This " pH jump" is a phenomenon which generally may be observed for reactions of hypochlorite with substrates that generate $CHCl_3$ by "haloform"-like reactions. Haloform test positive substrates such as acetone, 2-pentanone, acetophenone, and 5,5-dimethyl-1,3-cyclohexanedione show substantial pH jumps during hypochlorite reactions, whereas 3-pentanone, cyclohexanone, and 1-naphthol exhibit relatively stable pH behavior. The reaction–pH profile for acetone is shown in Figure 1.

When citric acid (1) was treated with hypochlorite under conditions similar to those used for acetone, the pH jump shown in Figure 1 also was observed. At fixed pH's, NMR studies revealed compound 1 to be more reactive with

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hypochlorite in neutral rather than basic solutions, a trend which parallels the pH-dependent efficiencies of chloroform production from 1.

It appears that oxidative decarboxylation is a general reaction of hypochlorite with suitably substituted organics in aqueous solution. (See Scheme I.) When 2-hydroxy-2-methylpropanoic acid (**3**) was treated with hypochlorite, not only did the pH jump shown in Figure 1 occur but also the reaction yielded $CHCl_3$, which was derived from the acetone produced when **3** underwent oxidative decarboxylation. Alternatively, when benzilic acid (**4**) and 2-hydroxy-2-ethylbutanoic acid (**5**) were subjected to hypochlorite reactions, benzophenone and 3-pentanone, respectively, were isolated in significant yields, reflecting oxidative decarboxylation in systems where subsequent $CHCl_3$ formation by way of the haloform reaction would not be expected.

The initial step of the chloroform-producing reaction of citric acid has been suggested to involve concurrent decarboxylation/oxidation at the tertiary, hydroxy carbon induced by hypochlorous acid.[2b] Halogenation/decarboxylation of the resulting acetonedicarboxylic acid would yield CO_2, $CHCl_3$, and pentachloroacetone isolated as ultimate products of this reaction. Oxidative decarboxylations of α-hydroxy carboxylic acids have been observed to result from the action of *N*-bromosuccinimide, bromine, and hypobromous acid, and acyl and/or alkyl hypobromites have been proposed as intermediates.[8-10]

The pH jump phenomenon is attributable to a stoichiometric effect resulting when covalently bound hydrogens are replaced during multiple halogenation steps. It is significant that 1,3-dihydroxybenzene (resorcinol), diethyl malonate, ethyl acetoacetate, and 2,4-pentanedione show rapid pH increases with hypochlorite similar to compound **2** under comparable conditions. Solutions of compounds **4** and **5** show no elevation of pH during hypochlorite-induced decarboxylation reactions.

Experimental Section

Organic substrates were obtained from commercial sources, except for benzilic acid, which was synthesized from benzil.[11] Melting points of solid reaction products and recrystallized (2,4-dinitrophenyl)hydrazone derivatives corresponded to values in the text cited in ref 11. Sodium hypochlorite solutions, except where noted, were derived from Clorox and were assayed by iodometric titration. Reaction pH measurements were obtained on an Orion 701 digital pH meter connected to a strip-chart recorder. Chromatographic analyses were performed with a DuPont 841 liquid chromatograph and an Aerograph 1520 gas chromatograph. Varian EM360A and EM390 spectrometers were used for NMR analyses; infrared and visible spectra were obtained with Perkin-Elmer 1420 and Bausch and Lomb Spectronic 20 spectrophotometers, respectively. Infrared and NMR spectra were matched with reference spectra.[12]

Reaction–pH profiles were obtained by using 50.0 mL of hypochlorite solutions stirred magnetically. The pH of the bleach was adjusted to 9.5 immediately prior to addition of substrates dissolved in water adjusted to pH 6–9.5 at concentrations indicated in Figure 1.

Reactions of 1,3-Dihydroxynaphthalene (2). Preparative scale reactions of compound **2** with hypochlorite were monitored for formation of phthalic acid by liquid chromatography, using terephthalic acid as internal standard. Typically, 1.6 g (0.010 mol) of substrate was added to 100 mL of Clorox with 350 mL of additional bleach added as aliquots over a 2–5-h period (5.25% NaOCl, 0.317 mol). Yields of phthalic acid approached maxima of 60–80% within 2–3 h. CO_2 production was measured in reactions by using 0.01 mol of substrate and 0.14 mol of hypochlorite mixed in an air-tight apparatus by a procedure described previously.[7] The yield of CO_2 was 60–80% after 5 h, based on theoretical conversion of one carbon of substrate.

Oxidative Decarboxylations of α-Hydroxy Acids. Citric Acid (1). Qualitative assessment of the reactivity of compound 1 as a function of pH was made by following the decay of the citric acid NMR absorption at δ 2.6 relative to 2,2-dimethyl-2-silapentane-5-sulfonate as an internal standard. Aliquots of Fisher 4–6% NaOCl (0.8 M) were diluted to 0.05 M and adjusted to pH 11.0–11.5 with NaOH, to pH 9.0–9.5 by addition of sodium borate, and to pH 7.2–8.0 by careful addition of dilute HCl. Solutions of 1 suitably adjusted in pH were added to make the initial NaOCl:citrate molar ratio 5–10 to 1. Compound 1 was found to be essentially inert at pH <11, and it had a half-life of several hours at pH 9. For pH 7.2–8.0 runs, addition of dilute HCl was required to counter pH jumps, and excess NaOH was added after 25–30 min to quench reactions. During this period, 50–75% of the citric acid was consumed, relative to a NaOCl:citrate reaction maintained at high pH with NaOH.

2-Hydroxy-2-methylpropanoic Acid (3). Sodium hypochlorite (50.0 mL, 0.8 M, adjusted to pH 8) was mixed for 50 min with 0.001–0.004 mol samples of 3 and extracted with 5.0 mL of dichloromethane. Analysis of the extract by colorimetry[13] and gas chromatography using bromotrichloromethane as internal standard confirmed the presence of chloroform yields of 8–17%. When equal molar amounts of the acid were mixed with hypochlorite at pH 9.5, the acetone NMR singlet at δ 2.1 was observed to grow at the expense of the substrate absorption at δ 1.3, and addition of (2,4-dinitrophenyl)hydrazine (in ethanol/H_2SO_4) resulted in 20% yields of acetone (2,4-dinitrophenyl)hydrazone.

Benzilic Acid (4). A 1.0-g (0.0044 mol) portion of 4 was added to 100 mL of 0.8 M bleach, and the solution effervesced and became cloudy. Extraction with dichloromethane and evaporation yielded 0.55 g (69% yield) of benzophenone, with identity confirmed by mp, infrared analysis, and conversion to the (2,4-dinitrophenyl)hydrazone.

2-Ethyl-2-hydroxybutanoic Acid (5). A 10.0-mL portion of 0.8 M sodium hypochlorite was adjusted to pH 9.4 with dilute HCl, and 0.39 g (7.8×10^{-4} mol) of 5 was added. The solution effervesced, and after 30 min, treatment with excess (2,4-dinitrophenyl)hydrazine in ethanol/H_2SO_4 gave a 20% crude yield of the 3-pentanone derivative identified by mp after recrystallization. Alternately, infrared analysis of a carbon tetrachloride extract of the α-hydroxy acid–hypochlorite reaction mixture confirmed the product of the reaction to be 3-pentanone.

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Registry No. 1, 77-92-9; 2, 132-86-5; 3, 594-61-6; 4, 76-93-7; 5, 3639-21-2; NaOCl, 7681-52-9; OCl⁻, 14380-61-1; acetone, 67-64-1; benzophenone, 119-61-9; 3-pentanone, 96-22-0; chloroform, 67-66-3; phthalic acid, 88-99-3.

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