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# Deiodination Kinetics of Water-Soluble Radiopaques

## YU-CHANG JOHN WANG

**Abstract** □ Deiodination of diatrizoic acid, an anionic radiopaque, was found to be catalyzed by Cu(II). Through a detailed study of o-iodobenzoic acid, a model compound, the copper-catalyzed $S_N1$ mechanism was established based on observations of common ion, salt, and pH effects. Meta- and para-iodobenzoic acids were unreactive. Deiodination thus was facilitated by a neighboring carboxylate that attracted copper. Iopamidol, a nonionic radiopaque, also underwent deiodination. At pH 7 or above, the hydroxide-ion substitution predominated. At pH below 7, the reaction is in favor of the copper-catalyzed $S_N1$ mechanism.

**Keyphrases** □ Diatrizoic acid—radiopaque, deiodination kinetics □ o-Iodobenzoic acid—deiodination, metal-catalyzed $S_N1$ mechanism □ Iopamidol—radiopaque, deiodination mechanism □ Kinetics—aromatic $S_N1$ deiodination of radiopaques □ Radiopaques—diatrizoic acid and iopamidol, deiodination kinetics □ Metal catalysis—neighboring carboxylate deiodination

The most important radiopaques are the water-soluble, anionic compounds such as diatrizoic acid (I), iothalamic acid, and iodipamide. These compounds are benzoic acid derivatives with two or three iodines attached to the benzene ring. There appears to be no evidence in the literature that appreciable deiodination occurs in products containing any of these compounds (1). However, experiments in these laboratories showed that significant deiodination took place in the absence of chelating agents.

Since the mechanism of this reaction was not established, this paper will discuss the deiodination kinetics of diatrizoic acid as a representative of anionic radiopaques. A model compound, o-iodobenzoic acid, was studied to support the proposed mechanism. A new nonionic radiopaque, iopamidol (II) (2), also was examined, and its deiodination kinetics were compared with those of diatrizoic acid.
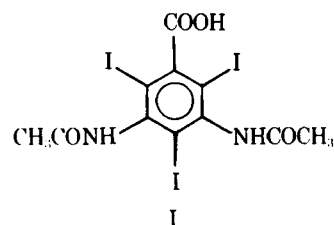
## EXPERIMENTAL

**Materials**—Diatrizoic acid[1], iopamidol[2], 8-hydroxyquinoline[3], and

[1] Renografin, E. R. Squibb & Sons, New Brunswick, N.J.
[2] $C_{17}H_{22}I_3N_3O_8$, N,N'-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-5-[(2-hydroxy-1-oxopropyl)amino]-2,4,6-triiodo-1,3-benzenedicarboxamide (Bracco 15,000, SQ 13,396), E. R. Squibb & Sons, New Brunswick, N.J.
[3] Eastman Kodak Co., Rochester, N.Y.



m- and p-iodobenzoic acids[3] were used without further purification; o-iodobenzoic acid[3] was recrystallized twice from ethanol–water. All other chemicals were reagent grade. The water used complied with the USP specifications for purified water.

**Deiodination of Diatrizoic Acid**—Diatrizoic acid was dissolved in water with a stoichiometric amount of sodium hydroxide. Sørensen phosphate buffer (3) was added to bring the final phosphate concentration to 0.0067 M. The chelating agent employed was edetate disodium USP at 0.04% (w/v). The amount of iodide produced after stressed conditions was determined by the USP method (4), which specifies the measurement of the absorbance of iodine in a toluene extract at 495 nm[4] after the iodide has been oxidized to iodine. The concentration was calculated from a standard curve obtained from potassium iodide solutions. Similar to the USP specification, the amount of iodide found was expressed as the percentage of the weight of iodide with respect to the weight of radiopaque in the same solution.

**Kinetic Studies for o-Iodobenzoic Acid**—o-Iodobenzoic acid was dissolved in water with a stoichiometric amount of sodium hydroxide. Sørensen phosphate buffer at 0.0067 M and cupric sulfate at 0.5 ppm of Cu(II) were used unless stated otherwise. Solutions were immersed in a constant-temperature (±0.1°) oil bath[5], and samples were removed periodically for UV assay. Absorbances of the samples at 295 nm were used



II
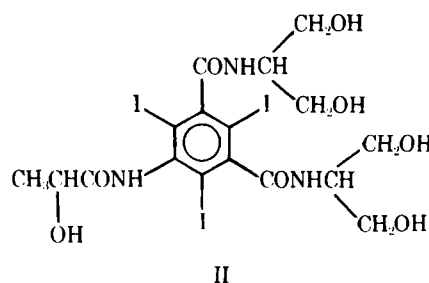
[4] Model 25 spectrophotometer, Beckman Instruments, Irvine, Calif.
[5] Constant-temperature circulator model FJ, Haake Inc., Saddle Brook, N.J.

**Table I—Production of Iodide from Diatrizoic Acid Solutions [a] at Various pH Values**

| pH | Iodide Found[b], % [c] |
|---|---|
| 7.8 | 0.371 |
| 7.4 | 0.388 |
| 7.0 | 0.333 |
| 6.6 | 0.227 |
| 6.2 | 0.150 |

[a] Solutions contained 20% (w/v) diatrizoic acid and 0.0067 M Sørensen phosphate buffer and were assayed after autoclaving at 120° for 30 min. [b] Unautoclaved samples and samples containing 0.04% (w/v) edetate disodium autoclaved at 120° for 30 min showed undetectable amounts of iodide (<0.0001%). [c] The weight percent of iodide with respect to the weight of diatrizoic acid in the same solution.

to calculate the amount of salicylic acid produced in the reaction. The residual amount of o-iodobenzoic acid, employed in the semilogarithmic plot, was obtained by subtracting the concentration of salicylic acid produced from the initial concentration of o-iodobenzoic acid. The reaction rates were calculated graphically from the initial slopes.

In one experiment, deiodination was followed simultaneously by three assay methods: the iodine assay, which was the same as for diatrizoic acid; the colorimetric assay, which measures the violet color produced by salicylic acid in the presence of ferric chloride; and the UV assay.

In another experiment, samples were analyzed by high-pressure liquid chromatography (HPLC) to identify the degradants produced in the kinetic study. The column was prepacked with reversed-phase Partisil ODS-2[6]. The mobile phase was methanol–water–phosphoric acid (48: 52:0.04). The UV detector[7] was operated at 240 nm. The flow rate[8] was 2 ml/min, and the volume of the injector[9] loop was 20 μl.

**Deiodination of o-, m-, and p-Iodobenzoic Acids**—Solutions of these compounds at 0.5 M were prepared by the addition of a stoichiometric amount of sodium hydroxide, 0.0067 M phosphate buffer, and 0.04 mM of Cu(II). After autoclave sterilization, the iodide content in these solutions was determined by the method described for diatrizoic acid.

**Deiodination of Iopamidol**—The reaction kinetics were followed by monitoring the iodide content. The solution pH values were maintained by 0.0067 M Sørensen phosphate buffer, and the iodide concentration was assayed by the procedure described for diatrizoic acid solutions.

Since the iodide ion produced by deiodination was much less than 1% of the iopamidol, a typical equation for first-order kinetics can be simplified (5) through approximation in an infinite series:

$$k_0 = \frac{1}{t} \log_e \frac{[\text{iopamidol}]}{[\text{iopamidol}] - [I_t]} = \left(\frac{1}{t}\right) \frac{[I_t]}{[\text{iopamidol}]} \quad \text{(Eq. 1)}$$
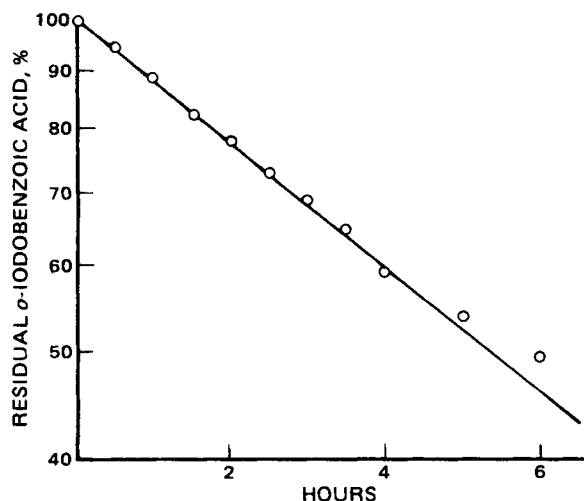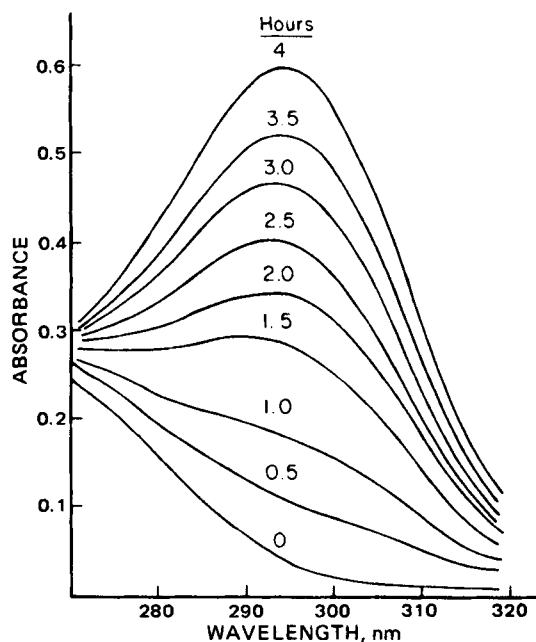


Figure 1—*Production of iodide (M) at 90° in 0.01 M diatrizoic acid solution containing 0.0067 M, pH 7 phosphate buffer and 4 ppm of Cu(II).*

[6] Whatman, Clifton, N.J.
[7] Model 1201 SpectroMonitor 1, Laboratory Data Control, Riviera Beach, Fla.
[8] Model 110A solvent metering pump, Altex, Berkeley, Calif.
[9] Model 7010 injection valve, Rheodyne, Berkeley, Calif.

Figure 2—*UV spectral changes due to the formation of salicylic acid from o-iodobenzoic acid (0.002 M). The numbers shown by the curves are the times elapsed in hours when the solution was studied at 90° and pH 7.*

where [iopamidol] is the initial concentration of iopamidol, $[I_t]$ is the iodide concentration at time $t$, and $k_0$ is the initial rate constant expressed in reciprocal time.

## RESULTS AND DISCUSSION

**Deiodination of Diatrizoic Acid**—To examine the effect of chelating agents, 20% diatrizoic acid solutions at various pH values were autoclaved at 120° for 30 min. Table I shows the production of the iodide content in solutions without a chelating agent. The iodide content, although small, exceeded the USP limit of 0.02%. Under the same conditions, preparations containing edetate disodium (0.04%) yielded undetectable amounts of iodide (<0.0001%). Therefore, it was concluded that in solutions without edetate, the trace amounts of heavy metals catalyzed the liberation of iodine from diatrizoic acid.

A spectrochemical analysis of water from the same source revealed a heavy metal content at the parts-per-billion level: Fe, 16; Cu, 9; Pb, 3; Ni, 1.4; and Zn, 37. The 0.0067 M phosphate buffer may contribute ~6 ppb or less of heavy metals. Since the USP limit for heavy metals for radiopaque compounds is 20 ppm, the majority of the heavy metal in the diatrizoic acid solution probably comes from the bulk compound; therefore, a heavy metal concentration in the parts-per-million range results.

To identify the metal responsible for catalysis, solutions of low metal content were obtained by extracting the same 20% diatrizoic acid solution at pH 7 with chloroform containing 0.1% 8-hydroxyquinoline. This solution was subdivided and spiked with 1 ppm each of Cu(II), Fe(III), and Fe(II) as the sulfate salt, Co(II), Zn(II), and Ag(I) as the nitrate salt, or Pb(II) as lead acetate. After autoclaving for 30 min, only the solution
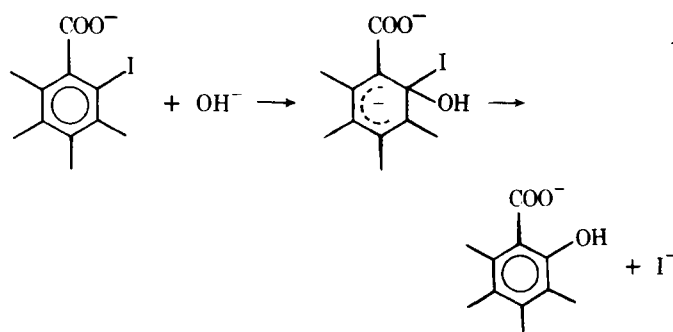


Scheme I—*$S_N2$ mechanism of deiodination*

**Table II—Deiodination Rate Constants for o-Iodobenzoic Acid**

| Experiment | Iodobenzoic Concentration, mM | [Cu(II)], ppm[a] | pH | Other Additives[b] | Temperature | $k_0$, hr$^{-1}$ |
|---|---|---|---|---|---|---|
| 1 | 2 | 0.5 | 7.0 | | 90° | 0.127[c] |
| 2 | 1 | 0.5 | 7.0 | | 90° | 0.121 |
| 3 | 0.4 | 0.5 | 7.0 | | 90° | 0.131 |
| 4 | 4 | 0.5 | 7.6 | 1.45 mM salicylic acid | 90° | 0.127 |
| 5 | 4 | 0.5 | 7.6 | | 90° | 0.127 |
| 6 | 4 | 0.5 | 8.0 | | 90° | 0.129 |
| 7 | 4 | 0.5 | 6.5 | | 90° | 0.118 |
| 8 | 2 | 5.08 | 7.0 | | 90° | 0.117 |
| 9 | 2 | 2.54 | 7.0 | | 90° | 0.116 |
| 10 | 2 | 1.27 | 7.0 | | 90° | 0.122 |
| 11 | 2 | 0.25 | 7.0 | | 90° | 0.127 |
| 12 | 2 | 0.2 | 7.0 | | 90° | 0.134 |
| 13 | 2 | 0.5 | 7.0 | 0.6 mM KI | 90° | 0.112 |
| 14 | 2 | 0.5 | 7.0 | 1.2 mM KI | 90° | 0.844 |
| 15 | 2 | 0.5 | 7.0 | 2.4 mM KI | 90° | 0.0739 |
| 16 | 2 | 0.5 | 7.0 | 20 mM NaBr | 90° | 0.126 |
| 17 | 2 | 0.5 | 7.0 | 100 mM KNO₃ | 90° | 0.174 |
| 18 | 2 | 0.5 | 7.0 | | 85.5° | 0.0589 |
| 19 | 2 | 0.5 | 7.0 | | 81° | 0.0462 |
| 20 | 2 | 0.5 | 7.0 | | 75.5° | 0.0165 |
| 21 | 2 | 0.5 | 7.0 | | 68° | 0.0054 |

[a] For Cu(II), 1 ppm is equivalent to 0.015 mM. [b] All solutions included 0.0067 M Sørensen phosphate buffer and a stoichiometric amount of sodium hydroxide. [c] The standard deviation of $k_0$ for Experiments 1–12 is 0.00577.



*Scheme II—S$_N$1 mechanism of deiodination*
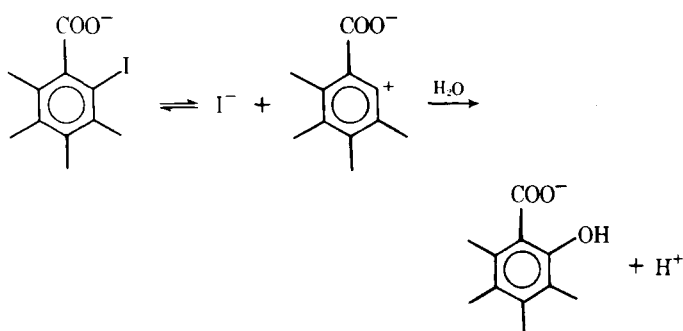
spiked with Cu(II) yielded a detectable iodide content. From these results, it is evident that Cu(II) catalyzed the deiodination of diatrizoic acid. By using a chelating agent such as edetate disodium, this reaction can be retarded.

To investigate the Cu(II)-catalyzed deiodination further, production of iodide in a diatrizoic acid solution was monitored as a function of time. Figure 1 shows the increasing iodide content as the solution was heated at 90°. By assuming that each diatrizoic acid molecule produces only one iodide ion, a semilogarithmic first-order plot (not shown) of the diatrizoic acid concentration versus time resulted in a significant curvature. To explain this deviation from first-order kinetics, the two possible mechanisms (6) for deiodination were examined.

*The S$_N$2 Mechanism*—At constant pH, the S$_N$2 mechanism (Scheme I) cannot explain the curvature observed in the first-order plot of diatrizoic acid. In addition, the deiodination of diatrizoic acid is independent of the pH between pH 6 and 8 (Table I), and that observation does not support a bimolecular reaction in which the hydroxide ion takes part in the rate-determining step.

*The S$_N$1 Mechanism*—The first step in the S$_N$1 mechanism (Scheme II), the rate-determining step, is the formation of carbonium ion. The iodide produced in the first step can inhibit further deiodination through the reversible reaction and thus accounts for the curvature observed in the semilog plot. In addition, this mechanism requires pH independence, which is consistent with the observed results. The aromatic S$_N$1 mechanism is well established for the dissociation of diazonium salts. However, for aromatic halides, even active ones, a unimolecular S$_N$1 mechanism has not been observed with certainty (7).

To obtain further support that an S$_N$1 mechanism is operative in deiodination, a simple model compound was studied because a diatrizoic acid contains other labile moieties such as anilide linkages that may perturb the reactivity of the molecule and complicate the mechanism. o-Iodobenzoic acid was selected for its structural similarity to radiopaque compounds in general. Furthermore, deiodination kinetics can be fol-

lowed by a simple UV assay of its deiodination product, salicylic acid, rather than by the more time-consuming iodide assay.

**Deiodination of o-Iodobenzoic Acid**—At neutral pH, o-iodobenzoic acid hydrolyzes to yield equal moles of salicylic acid, iodide, and the hydronium ion. Typical UV spectral changes are illustrated in Fig. 2. In one experiment, the reaction was followed by UV, colorimetric, and iodine assays, and the consistent results verified that deiodination of o-iodobenzoic acid, within experimental errors, produced only salicylic acid and iodide. This fact also was supported by the HPLC evidence shown in Fig. 3, in which only iodide and salicylic acid could be identified on the chromatogram. Figure 3 also shows that salicylic acid was stable under the conditions of the kinetic study, with decarboxylation, in particular, not taking place.

A semilogarithmic plot of the o-iodobenzoic acid concentration versus time shows that a typical reaction initially is rectilinear and finally exhibits definite exponential decline (Fig. 4). The pseudo-first-order rate constants, $k_0$, were calculated graphically from the initial slopes from:

$$\log_e \frac{A_0}{A_t} = -k_0 t \qquad \text{(Eq. 2)}$$

where $A_0$ and $A_t$ are the o-iodobenzoic acid concentrations at times zero and $t$, respectively. The time was measured in hours. Rate constants under various conditions are shown in Table II. In Experiments 1–3 and 5 in Table II, in which the initial concentration of o-iodobenzoic acid was varied, consistent rate constants further demonstrated that the reaction is first order with respect to the o-iodobenzoic acid concentration.

Since deiodination required Cu(II) as a catalyst, the reaction product, salicylic acid, might chelate copper, affect reaction rates, and thus cause a curvature in the semilog plot. Experiments 4 and 5 (Table II) showed that the reaction rate remained constant with excess salicylic acid. A Cu(II)–salicylate complex probably still is capable of catalyzing deiodination. The fact that deiodination is independent of pH between pH 6 and 8, as demonstrated with diatrizoic acid (Table I), also was shown by Experiments 5–8 (Table II).

The effect of the Cu(II) concentration was illustrated by Experiments 8–11 (Table II), which showed that the reaction seemed to be independent of the Cu(II) concentration between 0.25 and 5.08 ppm. Solutions spiked with Cu(II) in this concentration range resulted in essentially constant reaction rates. Without spiking, the reactions rates often were scattered, perhaps due to various amounts of Cu(II) introduced as impurities in water, buffer, or bulk compounds.

Addition of a small amount of potassium iodide greatly retarded deiodination. For the deiodination of o-iodobenzoic acid, iodide is the common ion. The magnitude of the common ion effect (8), $\alpha^{10}$, can be

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[10] The common ion effect can be used as strong evidence for a carbonium-ion intermediate. In deiodination reactions, the $\alpha$ value measures the relative reactivities of iodide and water to the carbonium ion. Generally, the more stable the intermediate carbonium is, the larger $\alpha$ is.
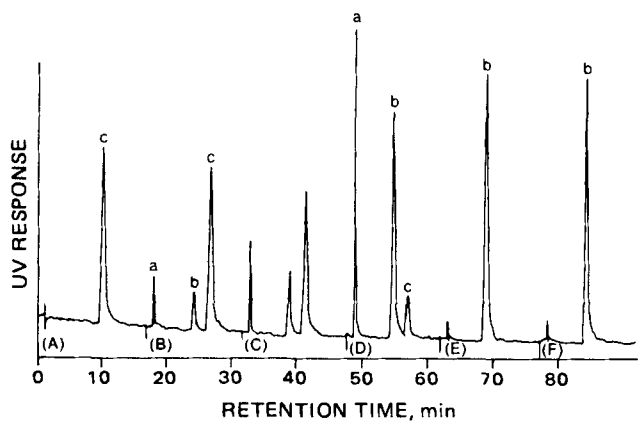
**Figure 3**—*High-pressure liquid chromatograms from kinetic studies of o-iodobenzoic acid (0.002 M) in pH 7 phosphate buffer and 4 ppm of Cu(II) at 90° for 0 hr (A), 1 hr (B), 2 hr (C), and 24 hr (D) and for salicylic acid under the same conditions for 0 hr (E) and 24 hr (F). Key: a, iodide; b, salicylic acid; and c, o-iodobenzoic acid.*
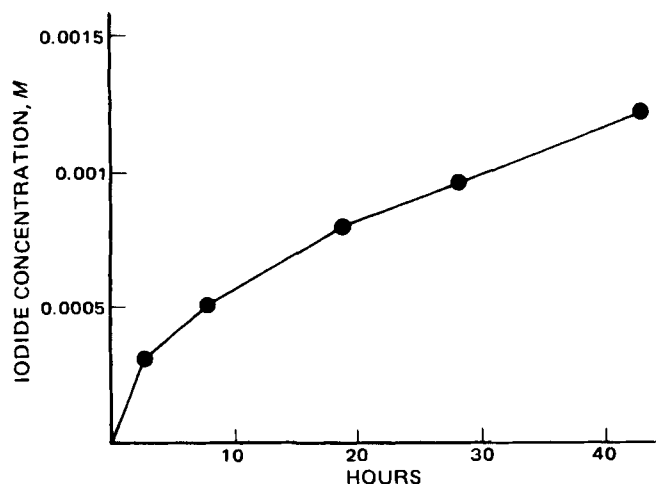
calculated from:

$$\alpha = \frac{1}{[I^-]} \left( \frac{k_0}{k_1} - 1 \right) \qquad \text{(Eq. 3)}$$

where $k_1$ is the initial rate constant with an added iodide concentration of $[I^-]$ and $k_0$ is the rate constant at $[I^-] = 0$.
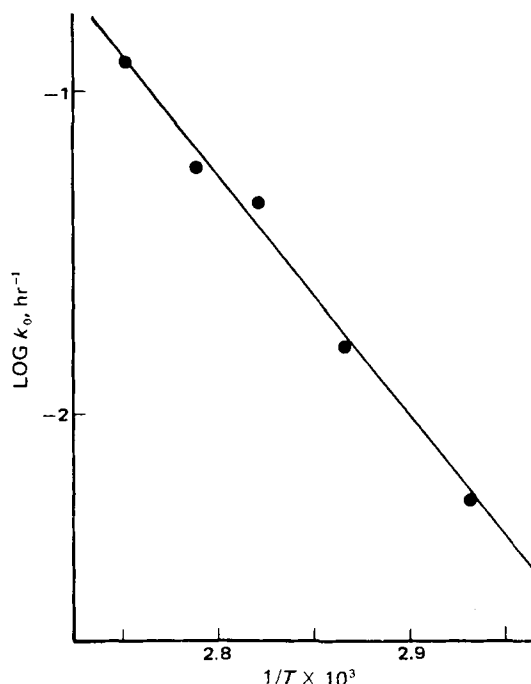
The $\alpha$ values for deiodination were 400 and 517 when the iodide concentrations were 1.2 and 2.4 mM, respectively. These values are on the same order of magnitude as the $\alpha$ values for the $S_N1$ hydrolysis of triphenylmethyl chloride (9). Such large $\alpha$ values for iodobenzoic acid lend strong support to the proposed $S_N1$ mechanism.

Addition of other halide ions, such as sodium bromide, did not affect reaction rates (Experiment 16). Increasing the ionic strength by adding large amounts of salt, such as potassium nitrate, enhanced deiodination (Experiment 17). These observations support an $S_N1$ mechanism. From an Arrhenius plot (Fig. 5) of the rate constants at five temperatures (Experiments 1 and 18–21), the heat of activation was calculated graphically to be 34 kcal/mole, which is comparable to many unimolecular $S_N1$ reactions (10).

**Deiodination of m- and p-Iodobenzoic Acids**—Apart from Cu(II) catalysis, deiodination is clearly of the $S_N1$ type for o-iodobenzoic acid. This reaction could be a unique instance of unimolecular aromatic substitutions in addition to the decomposition of diazonium ions. In the $S_N1$ mechanism, the neighboring carboxylate can function in either of two ways to facilitate the reaction. First, through electronic resonance effects, the negative carboxylate moiety could stabilize the formation of positive carbonium intermediates. If this were the case, p-iodobenzoic acid should undergo a reaction similar to o-iodobenzoic acid. Second, through a chelation effect, the carboxylate moiety could associate with copper ions, bringing them close to the reaction site and, perhaps, assisting the copper ion in polarizing the carbon–iodine bond. If this were the case, only o-



**Figure 5**—*Arrhenius plot of deiodination of o-iodobenzoic acid at pH 7.0 with Cu(II) catalysis.*

iodobenzoic acid would be reactive and the m- and p-analogs would not be.

Table III demonstrates that m- and p-analogs of iodobenzoic acid produced almost negligible amounts of iodide. The reaction rates of o-iodobenzoic acid and diatrizoic acid were comparable. These results ruled out any possible effect from electronic resonance and favored the second alternative of copper complexation by the *ortho*-carboxylate. This result also indicated that the two iodines adjacent to carboxylate in diatrizoic acid are most vulnerable to deiodination.

**Deiodination of Iopamidol**—The anionic radiopaque benzoic acid derivatives were examined in the previous sections. However, the newly developed nonionic radiopaques, due to a lack of negatively charged carboxylate moieties, tend to undergo deiodination *via* other mechanisms.



**Figure 4**—*First-order plot of deiodination of o-iodobenzoic acid.*
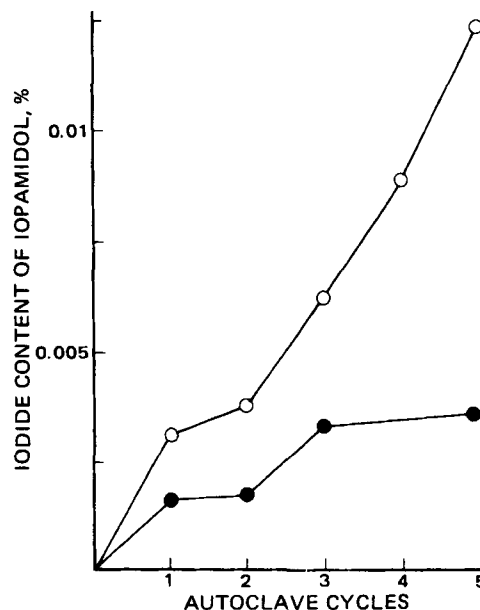


**Figure 6**—*Amount of iodide found in 20% iopamidol solution (pH 7, 0.0067 M phosphate buffer) subjected to various numbers of autoclave cycles. Each cycle was 90 min at 120°. Key: O, without chelating agent; and ●, with 0.04% edetate disodium.*

**Table III—Deiodination of Diatrizoic Acid and o-, m-, and p-Iodobenzoic Acids upon Autoclaving [a,b]**

| Compound | Iodide Produced, $M$ |
|---|---|
| Diatrizoic acid | 0.0397 |
| o-Iodobenzoic acid | 0.0452 |
| m-Iodobenzoic acid | 0.00001 |
| p-Iodobenzoic acid | 0.00003 |

[a] Solutions contained 0.5 $M$ compound, 0.04 m$M$ CuSO$_4$, and 0.0067 $M$ Sørensen phosphate buffer to maintain the pH at 7.6. [b] Samples were subjected to 30 min of autoclave sterilization at 120°.

An understanding of deiodination of this class of compounds is beneficial.

Deiodination of iopamidol was found to be extremely slow. To study the mechanism, samples had to be subjected to more drastic conditions, i.e., 90 min of 120° autoclave treatment. The production of iodide was plotted against the number of 90-min cycles (Fig. 6). In the range of ~0.01% or less, the iodide content could be considered rectilinear with respect to the number of cycles. The reaction rate can be calculated directly from the iodide content and reaction time. Figure 7 shows the semilogarithmic plot of the reaction rate constants at various pH values. In the absence of a chelating agent, thus probably causing the reaction to be catalyzed by copper, a plateau on the rate-pH profile suggests a predominant $S_N1$ mechanism that would be similar to the $S_N1$ mechanism already described.

In the presence of a chelating agent, such as edetate disodium, a unit slope on the pH-rate profile indicates that the reaction is dependent on the hydroxide-ion concentration and clearly suggests an $S_N2$ mechanism. The $S_N2$ mechanism becomes more important as the pH increases due to the increase of the hydroxide concentration. At pH values above 7.5, the $S_N2$ mechanism overshadows the $S_N1$ mechanism. The deiodination is predominantly a substitution of hydroxide ion and occurs regardless of the presence of a chelating agent.

The different behavior of diatrizoic acid and iopamidol can be summarized as follows. In diatrizoic acid, the carboxylate group promoted the $S_N1$ mechanism by drawing the copper ion closer to the reaction center or by stabilizing the carbonium charge. The $S_N2$ mechanism was completely inoperative because of the repulsion of hydroxide ion by the same negative charge. In iopamidol, the absence of carboxylate eased the attack by hydroxide ion, and thus the $S_N2$ mechanism was operable, although only in barely detectable rates. The Cu(II) ions catalyzed the deiodination of iopamidol; however, the $S_N1$ reaction was much slower than that of diatrizoic acid.

## CONCLUSION

This investigation was undertaken to determine the deiodination mechanism of certain water-soluble radiopaques. For the benefit of formulating injectable radiopaques, deiodination was examined only at neutral pH values. Evidence has been presented to show that, in anionic radiopaques, deiodination proceeds by an $S_N1$ mechanism, which also requires the assistance of neighboring carboxylate groups and Cu(II) ion. By studying a model compound, o-iodobenzoic acid, the high magnitude of the common ion effect, salt effect, pH independency, and high activation energy, characteristics of an $S_N1$ reaction, were observed. In nonionic radiopaques, because of the absence of negatively charged carboxylate, deiodination is facilitated by hydroxide ion. With trace
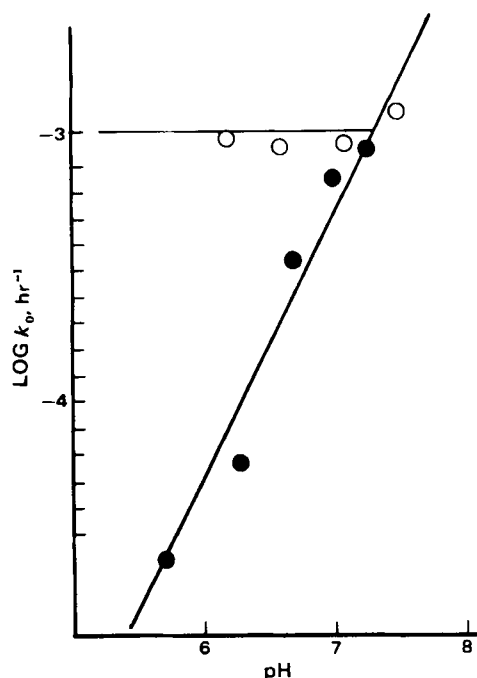


**Figure 7**—*Deiodination rate–pH profile for iopamidol in 0.0067* M *phosphate buffer at autoclave temperature. Key:* o, *without chelating agent; and* ●, *with 0.04% edetate disodium.*

metal, $S_N1$ deiodination of a nonionic radiopaque remains operative, although at a much slower rate than an anionic radiopaque.

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