

## Dehydration of Chloral Hydrate

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### *Abstract*

The reaction of chloral hydrate with various alcohols to form the corresponding hemiacetals was studied in the solvent acetone using nmr to follow the change in relative concentration of starting material and product. The reaction is acid-catalyzed. The rate-controlling step appears to be the dehydration of the hydrate to chloral. The effectiveness of benzoic acid and various substituted benzoic acids as catalysts does not correlate with the acid dissociation constants in water or aqueous alcoholic media.

The equilibria and kinetics of the hydration of carbonyl compounds and, to a lesser extent, the dehydration of carbonyl hydrates have been the subject of numerous investigations. Many references are included in a review of this subject by Bell (1). Most of the previous studies involved hydration (rather than dehydration) and were carried out in water or aqueous-organic solvents. The solvent systems with the least amounts of water were 92.5% acetone (2) and 95% dioxane (3).

The present research was initiated to study the dehydration of a stable hydrate (chloral hydrate) under conditions (a non-aqueous solvent) which would favor the greatest ratio of carbonyl compound to hydrate at equilibrium.

Preliminary to the present study the kinetics of the spontaneous conversion of chloral hydrate to chloral in solution in chloroform-d was followed by observing the increase in the nmr integration of the aldehyde proton. The kinetics were zero-order. The author tentatively interprets this as the result of a rapid equilibrium between chloral hydrate and chloral-water, favoring the hydrate, followed by a rate-determining separation of the water. A small layer of water on top of the chloroform was indeed noted when the nmr tube was inspected afterwards.

From the preceding it appeared necessary to use a solvent in which products of the dehydration, including water, would be soluble and to add a reactant which would react as rapidly and completely as possible with the chloral. Specifically, the solvents considered were dimethylsulfoxide-d<sub>6</sub>, acetone-d<sub>6</sub> and acetone. The choice of alcohols as the reactant afforded the important possibility of observing the effect of the structure of the alcohol, as well as its concentration, on the rate. If the reaction proceeds to the formation of chloral alcoholate (hemiacetal) via chloral as the rate-controlling step, one would predict that the rates will be little affected by the nature or concentration of the alcohol.

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<sup>1</sup>The experimental part of this research was done at the Application Laboratory, Naka Works, Hitachi Ltd., Ichige, Katsuta-shi, Ibaraki-Ken, Japan, while the author was on sabbatical leave from DePauw University.

### Experimental

Reagents: The absolute ethanol was first grade analytical reagent from Amakusa Kagaku Sangyo Co., Ltd. The following were first-grade analytical reagents from Wako Pure Chemicals Industries, Ltd.: chloral hydrate, t-butyl alcohol, i-propyl alcohol, p-dimethylaminobenzoic acid, p-nitrobenzoic acid. Special analytical reagent grade reagents from the same source were the following: acetone, benzoic acid, anthranilic acid and methyl alcohol. The chloral was from Tokyo Chemical Industries, Ltd. The acetone- $d_6$  and DMSO- $d_6$  were E. Merck A. G. spectrograde. All ingredients (except chloral hydrate) were anhydrous.

Kinetics: For each kinetic run the sample of chloral hydrate was weighed directly in an nmr tube. When a catalyst was used it was next weighed in the tube. Then a measured volume of solvent was added and the tube weighed again. When the solids had dissolved and the tube was at the probe temperature a measured volume of the alcohol was added and mixed. The alcohol was weighed at the end of the kinetic run. The tube was replaced in the probe and the nmr spectrum was run (the spectrum was repeated from time to time during each experiment). Data for calculating reaction rates were obtained by integrating the 5.5 to 4.5 region of the spectrum at suitable time intervals. With a few exceptions the rate data were obtained for at least 3 half-lives. The final spectrum and final integrations were run at *ca.* 9 half-lives. Since the total integration varied somewhat over the necessary time interval the progress of the reaction was taken from the ratio of the integration for the product to that for the starting material ( $\delta = 5.1 - 5.2$ ) plus that for the product ( $\delta = 4.8 - 4.9$ ). The data were obtained using Hitachi R-20-B and R-20-A nmr spectrophotometers. The probe temperatures<sup>2</sup> were 36.12 and  $36.05 \pm 0.01^\circ\text{C}$ , respectively, for these instruments.

Results: For the reaction between chloral hydrate and methyl, ethyl and i-propyl alcohols the first-order rate plots are linear in most cases (exceptions are noted) to at least 3 half-lives with random scatter of no more than  $\pm 0.01$  log unit, except for an occasional stray point. The final nmr spectrum is consistent with chloral alcoholate (hemiacetal) as the only product. For nearly all runs at least 40 experimental points were recorded and plotted. A typical rate plot is shown in Figure 1. With few exceptions the initial concentration of chloral hydrate was within the limits of 1.10 to 1.14 molar and all were within 1.00 to 1.33 molar. Within these limits the rates were independent of the initial concentration. In all cases the alcohol concentration was greater than that for the chloral hydrate. The effect of the nature of the alcohol and its concentration on the measured rate of the reaction and the position of equilibrium are given in Table 1. The percent of product at equilibrium is increased slightly in each case by increasing the ratio of alcohol to chloralhydrate. Also the percent product is favored a little by methyl *vs.* ethyl *vs.* i-propyl alcohol. Consistent with this the measured rates compared with those for ethyl

<sup>2</sup> These measurements were made with a calibrated thermistor resistance bridge. I thank Mr. Y. Ikebe for these measurements.

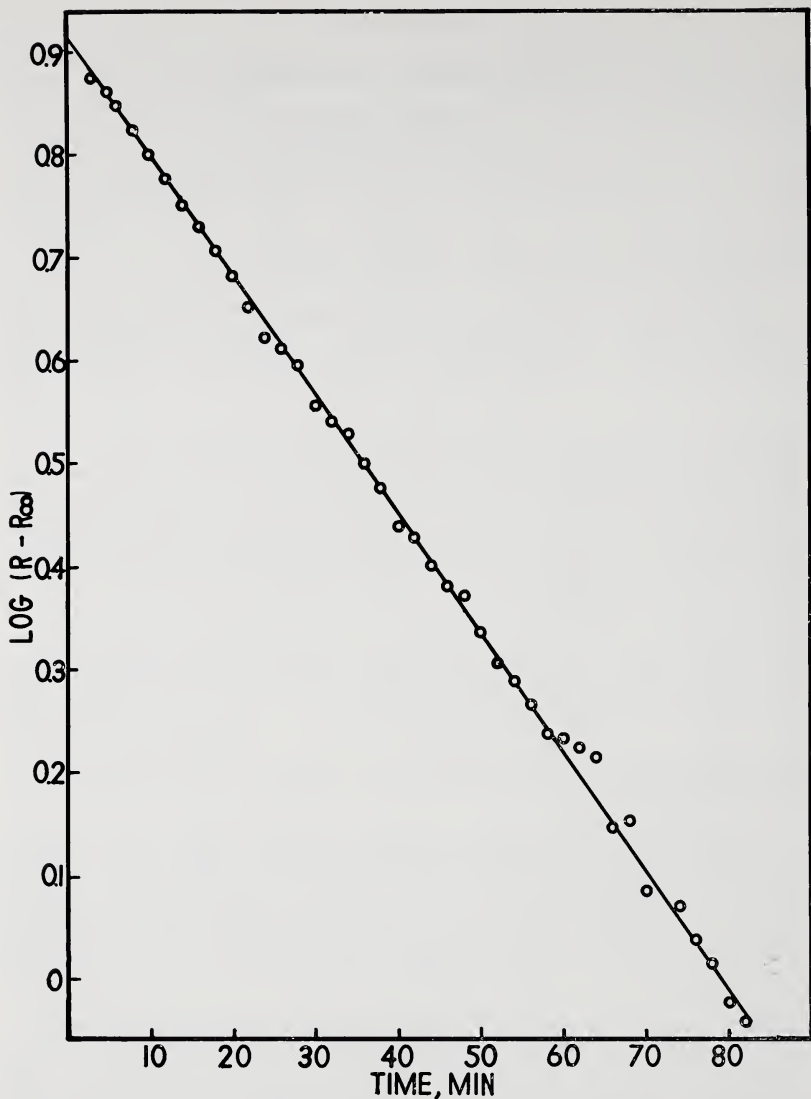


FIGURE 1. First order rate plot, using ratio ( $R$ ) of integration of chloral hydrate C-H Signal to the sum of the integration for that signal and the C-H product signal, for the reaction of chloral hydrate with ethyl alcohol in acetone as solvent and 0.061 moles of benzoic acid as catalyst.

alcohol are a little faster for the methyl alcohol and slower for the i-propyl. However, the important observations are that the rate difference between the three different alcohols is small; the rate difference with change in concentration of the ethyl alcohol is no more than experimental error (ca.  $\pm 0.03 \times 10^{-4}$ ) and is small for changes in the concentration of methyl and i-propyl alcohols; and the rate for

t-butyl alcohol is slower by at least an order of magnitude compared with that for the other three alcohols. Also for the t-butyl alcohol a peak at  $\delta:9.37$  showed 5–6% of chloral to be present at equilibrium.

TABLE 1. *The Rates of the Reaction of Chloral Hydrate with Alcohols in Acetone-d<sub>6</sub>.*

| ROH<br>R—                          | Moles of ROH/Mole<br>Cl <sub>3</sub> CCH(OH) <sub>2</sub> | k <sub>obsd</sub><br>x 10 <sup>4</sup> | % Completion at<br>Equilibrium (± 2%) |
|------------------------------------|---|--|---------------------------------------|
| CH <sub>3</sub>                    | 1.8   | 1.16 <sup>1</sup>                      | 88                                    |
| CH <sub>3</sub>                    | 2.4   | 1.20 <sup>1</sup>                      | 91                                    |
| CH <sub>3</sub>                    | 3.7   | 1.91 <sup>1</sup>                      | 93                                    |
| C <sub>2</sub> H <sub>5</sub>      | 1.8   | 1.11                                   | 84                                    |
| C <sub>2</sub> H <sub>5</sub>      | 2.3   | 1.06 <sup>2</sup>                      | 85                                    |
| C <sub>2</sub> H <sub>5</sub>      | 3.0   | 1.08                                   | 92                                    |
| (CH <sub>3</sub> ) <sub>2</sub> CH | 1.9   | 0.54 <sub>3</sub>                      | 77                                    |
| (CH <sub>3</sub> ) <sub>2</sub> CH | 3.3   | 0.74                                   | 80                                    |
| (CH <sub>3</sub> ) <sub>3</sub> C  | 2.7   | ca. 0.025 <sup>-4</sup><br>0.035       | ca. 55 <sup>4</sup>                   |

<sup>1</sup> For a short time at the beginning each of these reactions proceeded at a rate of 75–82% of the rate given.

<sup>2</sup> Acetone rather than acetone-d<sub>6</sub> was the solvent.

<sup>3</sup> At the beginning this reaction proceeded at a rate double the rate reported.

<sup>4</sup> These results are very approximate because the CH triplet (S = 5.20) of the chloral hydrate and the CH of the product so overlap that the rate could not be followed by the integration, although it was qualitatively obvious that the reaction was going very slowly. The numbers are obtained from the relative height of a developing singlet peak 0.12 ppm downfield from the CH peak of the t-butyl alcohol. This new peak was presumed to be the CH peak of the t-butyl group in the product.

t-Butyl alcohol reacted with chloral (not the hydrate) at a moderate rate, whereas the other three alcohols reacted so rapidly that the reactions were finished by the time the nmr tubes were placed in the instrument. The rate constant for the reaction with t-butyl alcohol was not measured (about one-half of the chloral had reacted in 80 min.). Qualitatively the rate difference was so striking that measurement of this rate was of no importance.

The rate of the reaction between chloral hydrate and ethyl alcohol in acetone was increased by the addition of acid. The results for benzoic acid and substituted benzoic acids as catalyst are summarized in Table 2. For each of the acids the rate is proportional to the amount of acid. The slope of the best straight line through a plot of k<sub>obsd</sub> x 10<sup>4</sup> vs. moles of acid x 10<sup>2</sup> is recorded for each acid in Table 2. A sample plot (for benzoic acid) is shown in Figure 2. The slope is a measure of the relative catalytic effectiveness of each acid as a catalyst.

As was true of the uncatalyzed reactions, the rates of the acid-catalyzed reactions are independent of the initial concentration of chloral hydrate.

In the case of each of the acid-catalyzed reactions a small singlet at  $\delta:9.37$  was observed in the initial spectrum before the alcohol was added. Integration of this signal indicated the presence of  $5 \pm 1\%$  of chloral. For the uncatalyzed reactions this signal was not observed

unless the mixture was allowed to stand for a longer time before the alcohol was added. In all cases, except for *t*-butyl alcohol, this peak disappeared within a few minutes after adding the alcohol.

### Discussion

For the reaction of chloral hydrate with alcohols a rate-controlling step which precedes the reaction of some intermediate with the alcohol

TABLE 2. *The Rates<sup>1</sup> of the Reaction of Chloral Hydrate with Ethyl Alcohol Catalyzed By Benzoic Acid and Substituted Benzoic Acids.*

| X-PhCOOH<br>X is            | Moles ArCOOH x 10 <sup>2</sup>  | k <sub>obsd</sub> x10 <sup>4</sup> 2,3 |      |
|-----------------------------|---|--|------|
|                             | 1.9   | 1.74                                   |      |
|                             | 4.5   | 2.61                                   |      |
|                             | 5.3   | 2.87                                   |      |
|                             | 8.0   | 3.84                                   |      |
|                             | 11.0  |  | 4.69 |
|                             | 12.6  |  | 5.84 |
|                             | Slope <sup>4</sup> = 0.351 (Av. dev. = 0.008)                             |  |      |
| H                           | 2.0   | 1.91                                   |      |
|                             | 2.1 <sup>5</sup>  |  | 2.18 |
|                             | 4.2 <sup>5</sup>  |  | 2.80 |
|                             | 6.1   | 3.85                                   |      |
|                             | 6.0   | 4.03                                   |      |
|                             | 6.1   | 3.92                                   |      |
|                             | 11.0 <sup>5</sup>   |  | 6.01 |
|                             | 12.5  | 7.00                                   |      |
|                             | Slope <sup>4</sup> = 0.466 (Av. dev. = 0.007)                             |  |      |
| <i>o</i> -NO <sub>2</sub>   | 2.8   | 2.52                                   |      |
|                             | 5.0   |  | 3.57 |
|                             | 7.4   |  | 4.91 |
|                             | 10.0  |  | 6.00 |
|                             | Slope <sup>4</sup> = 0.502 (Av. dev. = 0.004)                             |  |      |
| <i>p</i> -Cl                | 2.4   | 2.16                                   |      |
|                             | 3.9   | 3.04                                   |      |
|                             | 4.9   | 3.56                                   | 3.58 |
|                             | 6.7   | 4.58                                   | 4.76 |
|                             | 9.0   | 5.57                                   |      |
|                             | 10.1  |  | 6.02 |
|                             | 11.2  |  | 5.80 |
|                             | Slope <sup>4</sup> = 0.502 (Av. dev. = 0.013 or 0.005 without last point) |  |      |
| <i>p</i> -NO <sub>2</sub>   | 2.0   | 2.13                                   |      |
|                             | 3.9   | 3.03                                   |      |
|                             | 4.3   | 3.37                                   | 3.34 |
|                             | 5.5   | 3.83                                   | 3.78 |
|                             | 5.6   | 3.99                                   | 3.91 |
|                             | 6.6   | 4.37                                   | 4.30 |
|                             | 9.3   |  | 6.22 |
|                             | 10.4  |  | 6.30 |
|                             | Slope <sup>4</sup> = 0.514 (Av. dev. = 0.005)                             |  |      |
| <i>p</i> -CH <sub>3</sub> O | 2.2   | 2.37                                   |      |
|                             | 4.8   | 3.88                                   |      |
|                             | 6.8   | 5.46                                   | 5.22 |
|                             | 7.1   | 5.90                                   | 5.68 |
|                             | 9.3   | 6.26                                   | 6.30 |
|                             | Slope <sup>4</sup> = 0.563 (Av. dev. = 0.011)                             |  |      |



|                                      |     |      |
|--------------------------------------|-----|------|
| p-(CH <sub>3</sub> ) <sub>2</sub> N- | 1.9 | 2.32 |
|                                      | 2.2 | 2.73 |
|                                      | 2.3 | 2.92 |
|                                      | 3.0 | 3.45 |
|                                      | 4.6 | 4.65 |
|                                      | 5.9 | 5.96 |
|                                      | 6.1 | 6.18 |
|                                      | 7.3 | 6.75 |

Slope<sup>4</sup> = 0.780 (Av. dev. = 0.008)

<sup>1</sup> For all kinetic runs the amounts used were within the following limits: chloral hydrate, 0.908-0.982  $\times 10^{-3}$  moles; ratio of moles of ethyl alcohol to moles of chloral, 1.96-2.39; weight of acetone, 0.4866-0.5015 g or acetone-d<sub>6</sub>, 0.5265-0.5659 g. The per cent completion of the reaction at equilibrium was 82-86% ( $\pm 2\%$ ).

<sup>2</sup> The rate of the forward reaction in each case is greater than the measured rate (which is that given in this Table) because the measured rate is the algebraic sum of the forward and reverse reactions. It is considered that the *comparison* of the measured rates is valid because the equilibrium position is nearly the same for all cases.

<sup>3</sup> The rates in the right-hand column were calculated using the change of peak height of the substrate C-H peak and product C-H peak. In those cases in which there is a number only in the right-hand column integration was not satisfactory due to a broad O-H peak in the region of interest. Justification for the use of peak height is provided (for the cases in which there are two numbers) by comparing the numbers in the right-hand column with those in the left which were obtained from integration.

<sup>4</sup> The slope for each acid is from the best straight line through a plot of rate  $\times 10^{-4}$  vs. moles of acid  $\times 10^{-2}$ . The intercept at zero-time is the same for all plots.

<sup>5</sup> The solvent was acetone-d<sub>6</sub>.

in a fast step is supported by the following observations: (1) the kinetics are first-order, (2) the rate is nearly the same for methyl, ethyl and i-propyl alcohol, (3) the rate is changed only a little upon changing the relative amount of the alcohol (See Table 1) and, (4)

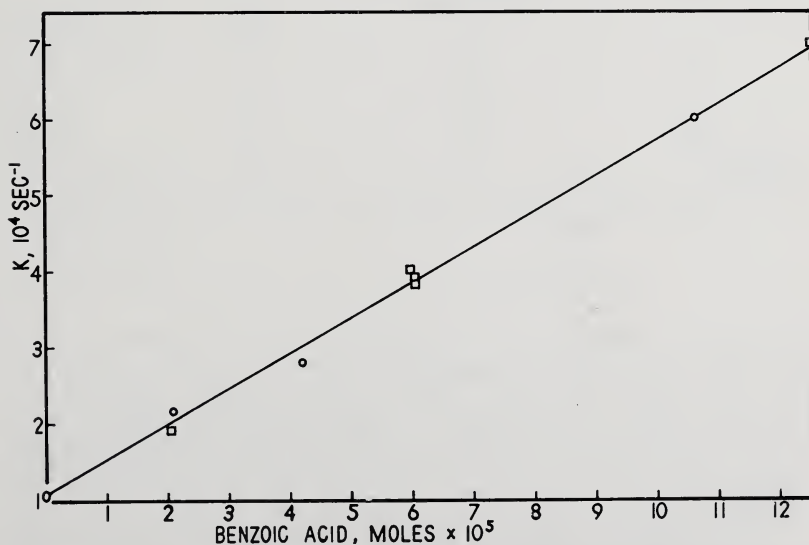
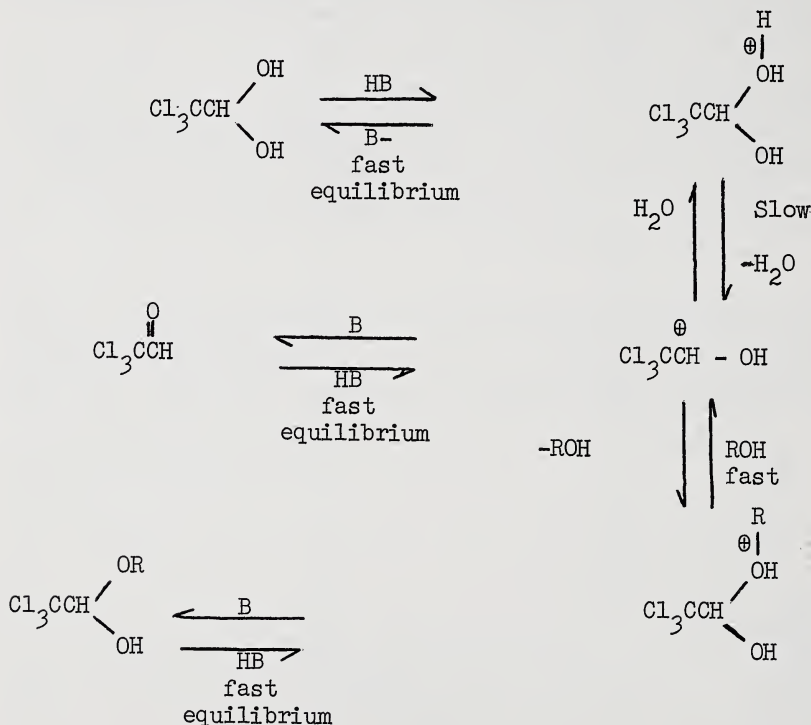


FIGURE 2. Plot of rates of formation of chloral alcoholate from chloral vs. amount of benzoic acid. Solvent: O acetone-d<sub>6</sub>, □ acetone.

the very rapid reaction of the alcohols with chloral. The small effect on the rate of changing the alcohol concentration may be, in part, due to a change in the nature of the medium.

In addition to the preceding facts, the similarity of the structure of the hydrate to that of acetals and the fact that the reaction is acid-catalyzed (See Table 2) suggests a mechanism similar to the hydrolysis of acetals (6). The observation of about five per cent of chloral in equilibrium with the hydrate in acetone (or acetone- $d_6$ ) after a sufficient length of time also supports the proposal that chloral may be formed as an intermediate in the rate-controlling step. The mechanism shown below is consistent with all of the facts. Rapid equilibrium between chloral and its conjugate acid is predicted. Hence,



although the conjugate acid is written as the intermediate, it is reasonable that one observe chloral when there is no alcohol present or when the alcohol reacts only slowly (t-butyl alcohol). Moreover, the observation that the nmr signal for chloral appeared quickly (before adding the alcohol) for all cases in which acid was present but was slower in the absence of acid is also consistent with the proposed mechanism.

This mechanism proposes that the rate-controlling step for the formation of both chloral and its hemiacetal is the same except for the t-butyl alcohol. For the "uncatalyzed" reactions the chloral hydrate

may act as proton donor. The pK of chloral hydrate in water is reported to be 10.04 (4). It is proposed that the rate being measured in each case, except for t-butyl alcohol, is the rate of dehydration of chloral hydrate.

It was anticipated that the catalytic effectiveness of the acids would correlate with their acidities. However, this was not observed as shown in Table 3 in which the acidities are reported for the acids in aqueous or aqueous alcoholic solutions or in dimethylsulfoxide (10, 11). The lack of correlation probably results from different degrees of intramolecular, intermolecular and solvent-solute interactions (e.g., hydrogen bonding) in the different solvents. The difference in relative acidities of the acids (Table 3) in water or aqueous alcoholic solution vs. those in dimethylsulfoxide make a striking comparison. A less striking difference is noted by Dippy (7) for the order of acid dissociation in methyl, ethyl or butyl alcohols ( $p\text{-NO}_2 > p\text{-Cl} > p\text{-CH}_3\text{O} > \text{H}$ ) compared with water ( $p\text{-NO}_2 > p\text{-Cl} > \text{H} > p\text{-CH}_3\text{O}$ ). Unfortunately, the relative acidities of these acids are not reported in acetone.

In summary, the measured rates of formation of hemiacetals (except with t-butyl alcohol) afford a method for measuring the rate of dehydration of chloral hydrate to chloral. The reaction is first-order and is acid catalyzed.

TABLE 3. Comparison of Catalytic Effectiveness with Acidities for Substituted Benzoic Acids.

| X-PhCOOH                            | Relative Catalytic Effectiveness | Relative Acidity in water or Aqueous Alcohol | Relative Acidity <sup>4</sup> in dimethylsulfoxide |
|-------------------------------------|----------------------------------|--|--|
| X is                                | $R_X / R_H$                      | $K_X / K_H$                                  | $K_X / K_H$  |
| o-NH <sub>2</sub>                   | 0.74                             | 0.17 <sup>1</sup>                            |  |
| H                                   | 1.00                             | 1.00   | 1.00   |
| o-NO <sub>2</sub>                   | 1.06                             | 6.30 <sup>2</sup>                            | 0.75   |
| p-Cl                                | 1.06                             | 6.00 <sup>3</sup>                            | 0.92   |
| p-NO <sub>2</sub>                   | 1.09                             | 1.69 <sub>3</sub>                            | 0.82   |
| p-CH <sub>3</sub> O                 | 1.19                             | 0.54 <sup>3</sup>                            | (1.05 C <sub>2</sub> H <sub>5</sub> O)             |
| p-(CH <sub>3</sub> ) <sub>2</sub> N | 1.66                             | 0.15 <sup>3</sup>                            | (1.16 p-NH <sub>2</sub> )                          |

<sup>1</sup> Calculated from dissociation constants given by Brown et al (5).

<sup>2</sup> From Hine (8).

<sup>3</sup> From Hine (9).

<sup>4</sup> From Kolthoff, et al (10) and Ritchie, et al (11).

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