Sterically Hindered Benzoic Acid Derivatives

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The base-catalysed hydrolysis of 2,4,6-tribromo-benzoyl- and 2,4,6-triiodobenzoyl chloride in 65 % dioxane/water at 5 °C was investigated. The rate constants found were $k_2=0.15$ l mol^{-1} min^{-1} and $k_2=0.03$ l mol^{-1} min^{-1}, respectively. The behaviour of 2,4,6-triiodobenzoic acid in concentrated sulfuric acid was examined. Simple protonation was shown to occur, corresponding to an i-factor of 2. 4-Nitrophenyl 2,4,6-tri-bromo- and 4-nitrophenyl 2,4,6-triiodobenzoate were hydrolyzed in 56 % dioxane/water at 30 °C and the constants were determined to be $k_2=0.469$ l mol^{-1} min^{-1} and 0.070 l mol^{-1} min^{-1}, respectively.

During a search for stable aroyl thiocyanates [1] our attention was focused on 2,4,6-tribromo- and 2,4,6-triiodobenzoic acid. We have shown that the corresponding acid chlorides react smoothly with 1,2,3,4-thiatriazole-5-thiolate in aqueous acetone at 0 °C to yield 5-aroylthio-1,2,3,4-thiatriazole.[1]

However, according to the literature 2,4,6-tribromobenzoyl chloride is a very unreactive acid chloride, surviving boiling aqueous sodium hydroxide for an extended period of time.[2] This observation is surprising since in the same paper a good yield of the methyl ester was obtained by boiling a methanolic solution of the acid chloride. Furthermore, the solvolysis in methanol at 25 °C has been found to proceed with $k=1.86 \times 10^{-4}$ min^{-1}.[3] From the data in Ref. 2 it appears that the rate of hydrolysis is zero order in 2,4,6-tribromobenzoyl chloride concentration. Since this reaction was carried out heterogeneously we are inclined to believe that these measurements reflect the velocity of solution of the acid chloride in water or aqueous base rather than the rate of hydrolysis.

Solvolysis experiments have now been carried out in mixtures of water and dioxane where the reaction could be made homogeneous. The rate of basic hydrolysis was determined by quenching the reaction with excess hydrochloric acid at various time intervals followed by titrimetric determination of the acid in excess. This method is justified if the rates of neutral or acid-catalyzed solvolysis are negligible compared to the base-catalyzed reaction. This was true both for 2,4,6-triiodobenzoyl and 2,4,6-tribromobenzoyl chloride, whereas, e.g., 4-nitro-2,6-dimethylbenzoyl chloride reacts so fast in basic as well as neutral and acidic media, that this method was not justified.[4] Another limitation of this method is that the reactions studied should be slow enough to allow concentration determinations early in the reaction. In this work the latter restriction could be overcome by running the reaction at 5 °C.

We found that both above-mentioned acid chlorides upon base catalyzed hydrolysis in 65 % (V/V) dioxane at 5 ± 1 °C displayed second order kinetics. The values found were $k_2=0.15$ l mol^{-1} min^{-1} for 2,4,6-tribromobenzoyl chloride and $k_2=0.03$ l mol^{-1} min^{-1} for 2,4,6-triiodobenzoyl chloride. As would be expected for steric reasons the rate constant of 2,4,6-tribromobenzoylchloride has a higher value than the one of 2,4,6-triiodobenzoyl chloride.

Having established the S$_N$2 reactivity of these compounds we turned to investigate the possible S$_N$1 reactivity. Formation of 2,4,6-triiodobenzoylium ion from any derivative of this species would result in steric relief. Furthermore the inductive effect of the iodine atoms, which presumably would retard the development of a positive charge on the carbonyl carbon in the transition state, is likely to be small (according

to Pauling the electronegativity of I is 2.5 which is the same as that of C). Mesomeric effects of the iodine atoms would tend to stabilize the developing charge in the transition state.

To establish whether 2,4,6-triiodobenzoylium ion is formed from the parent acid in concentrated sulfuric acid, we have carried out cryoscopic measurements in this solvent.[5] Within the experimental uncertainty van't Hoff's i-factor never exceeded 2, even after 47 h at room temperature, meaning that only simple protonation occurs. Chemical evidence substantiated the physical measurements. When the solutions of 2,4,6-triiodobenzoic acid in concentrated sulfuric acid were poured into cold methanol, no trace of the methyl ester could be detected in the product, which always consisted of the pure acid.

Esters of 2,4,6-trihalobenzoic acid are readily accessible from the reaction of the acid chlorides and alkoxide or phenoxide ions. These esters are stable under neutral and acid conditions. Under basic conditions, however, they are hydrolyzed, alkyl esters slowly but aryl esters easily. If another alcohol is present transesterification occurs. If, $e.g.$, methyl 2,4,6-triiodobenzoate is dissolved in ethanol containing ethoxide ions, ethyl 2,4,6-triiodobenzoate appears in the reaction mixture (60 % after 24 h at room temperature), or if the 2-octyl ester is recrystallized from methanol containing traces of strong base, the ester is partly transformed to the methyl ester.

The hydrolysis at 30 °C of 4-nitrophenyl 2,4,6-triiodobenzoate and 4-nitrophenyl 2,4,6-tribromobenzoate in 56 % (V/V) dioxane with hydroxide ions obeys second order kinetics.[6] The rate determination were run under pseudo-first-order conditions. The rate was followed by continuous UV recording of the absorption at 406 nm, which is λ_{max} for the 4-nitrophenoxide ion in 56 % dioxane. In both cases the reaction mixtures exhibit isosbestic points, 4-nitrophenyl 2,4,6-tribromobenzoate at 238 nm and 316 nm, and 4-nitrophenyl 2,4,6-triiodobenzoate at 300 nm. From a plot of the observed pseudo-first-order rate constants $versus$ hydroxide ion concentration at 30 °C the second-order rate constant was evaluated to be $k_2 = 0.469$ l mol⁻¹ min⁻¹ for 4-nitrophenyl 2,4,6-tribromobenzoate (initial concentration $= 0.945 \times 10^{-4}$ mol l⁻¹) and

$k_2 = 0.070$ l mol⁻¹ min⁻¹ for 4-nitrophenyl 2,4,6-triiodobenzoate (initial concentration 0.084×10^{-4} mol l⁻¹). Using the same technique, we found that in 1 N hydrochloric acid and in neutral solution no hydrolysis has occurred even after 4 days.

EXPERIMENTAL

Hydrolyses of acid chlorides (neutral and acid conditions). Approximately 5×10^{-2} M solutions of 2,4,6-tribromobenzoyl or 2,4,6-triiodobenzoyl chloride in 70 % (V/V) dioxane were left for 120 min at room temperature. Titration with 0.1 M sodium hydroxide showed no base consumption. In the case of the iodo compound even after 22 h at room temperature the base consumption was negligible. Similar results were found for the reaction in acid media. A solution of 4-nitro-2,6-dimethylbenzoyl chloride (5.26×10^{-2} M in 65 % dioxane) released hydrochloric acid so fast that the titration procedure could not be used. This was also the case in acid solution.

Hydrolyses of acid chlorides (basic conditions). About 4 mmol of the acid chloride was dissolved in 65 ml of dioxane. 20 ml of a 0.5000 N sodium hydroxide solution was added, and the solution was made up to 100 ml with water. The temperature of the reaction mixture was kept at 5 °C. The rate was followed by adding 5 or 10 ml aliquots of the solution to 20 ml of 0.1000 N hydrochloric acid. Back titration determined the consumption of sodium hydroxide in the hydrolysis. By means of these data, the concentration of base and acid chloride was determined. Second-order rate constant was evaluated from the plot of $\ln[(B_0 - x)/(A_0 - x)]$ against time. B_0 and A_0 are initial base and acid chloride concentrations, respectively.

Cryoscopic technique. Cryoscopic measurements were carried out as described by Newman et $al.$,[5] using the same type of freezing-point cell. An ordinary Beckmann mercury thermometer was used, and stirring was effected by means of a magnetic stirrer.

4-Nitrophenyl 2,4,6-trihalobenzoate. To a solution of 5 mmol of 2,4,6-trihalobenzoyl chloride in 100 ml of acetonitrile was added a solution of 8 mmol (1.43 g) of sodium 4-nitrophenolate in 100 ml of the same solvent. The reaction mixture was refluxed for 1 h. After filtration and evaporation of the solvent, the crude product was dissolved in diethyl ether. The solution was washed several times with water, dried over sodium sulfate, and evaporated. Recrystallization from ether gave the pure product.

4-Nitrophenyl 2,4,6-tribromobenzoate. Yield: 75 %. M.p.: 132—133 °C. (Found: C 32.62; H 1.40; N 2.87; Br 49.75. Calc. for $C_{13}H_6NO_4Br_3$: C 32.52; H 1.25; N 2.92; Br 49.97.) UV: $\lambda_{max} = 265$ nm, $\varepsilon = 3.2 \times 10^3$ (60 % dioxane/water).

4-Nitrophenyl 2,4,6-triiodobenzoate. Yield: 71 %. M.p.: 153.5−154.5 °C. (Found: C 25.05; H 1.01; N 2.17; I 61.20. Calc. for $C_{13}H_6NO_4I_3$: C 25.15; H 0.97; H 2.25; I 61.35). UV: $\lambda_{max}=239$ nm, $\varepsilon=2.3\times10^4$. $\lambda_{max}=264$ nm (shoulder), $\varepsilon=1.1\times10^4$ (60 % dioxane/water).

Basic hydrolysis of 4-nitrophenyl 2,4,6-trihalobenzoate in 56 % (V/V) dioxane. Procedure for kinetic runs. Stock solutions of the ester (approx. 1×10^{-4} M) and sodium hydroxide were prepared in 56 % (V/V) dioxane. Twenty ml of the ester stock solution was mixed with various amounts of the sodium hydroxide and the volume was made up to 25 ml. The solution was then approx. 0.8×10^{-4} M in ester and 0.2−0.02 M in sodium hydroxide. The rate of hydrolysis was followed at 30 °C by continuous measurements of the absorbance at 406 nm. Plots of log $(A_\infty-A)$ vs. time were always linear. From the slope of these curves, pseudo-first-order rate constants were determined. The second-order rate constant was obtained from the slope of a plot of the observed pseudo-first-order constant vs. hydroxide concentrations. The apparatus used was a UNICAM SP 1800 UV-VIS Spectrophotometer.

Trans-esterification of methyl 2,4,6-triiodobenzoate. A 5 % solution of methyl 2,4,6-triiodobenzoate in ethanol containing 0.2 N ethoxide ion was allowed to stand for 24 h. NMR showed that about 60 % of the methyl ester was converted to the ethyl ester.

Trans-esterification of 4-nitrophenyl 2,4,6-triiodobenzoate. When a 5 % solution of this ester in ethanol containing 0.1 N KOH was allowed to stand for 24 h, NMR analysis showed complete conversion to the ethyl ester.

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