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Keyphrases

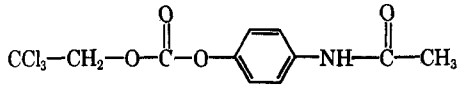
Coumarins
Columbianin structure—revised
Column chromatography—separation
IR spectrophotometry—structure
Mass spectrometry—structure
Paper chromatography—identity
TLC—identity
NMR spectrometry—identity
Polarimetry—identity

4-Acetamidophenyl 2,2,2-Trichloroethyl Carbonate Synthesis, Physical Properties, and *In Vitro* Hydrolysis

By J. V. SWINTOSKY*, H. C. CALDWELL, C. W. CHONG, G. M. IRWIN, and L. W. DITTERT*

A trichloroethyl carbonate prodrug ester of acetaminophen has been made by reacting acetaminophen with trichloroethyl chloroformate. It is a virtually tasteless crystalline compound retaining the pharmacologic effects of acetaminophen and trichloroethanol. It is lipophilic; its solubility in water is less than 0.05%. It undergoes base-catalyzed hydrolysis, and at pH 7.4 has a half-life in water solution of about 7 hr. Its stability in the solid state makes this compound amenable to use in dosage forms such as tablets and capsules. Hydrolysis of this compound is not catalyzed by human gastric fluid, but it is catalyzed by human intestinal fluid, rat intestinal mucosa, rat plasma, rat liver, and human plasma. It was surmised, therefore, that following oral administration to animals, a portion of the prodrug may be absorbed intact, but some cleavage may occur before and during absorption from the intestines. Furthermore, since enzymes that hydrolyze it are prevalent in plasma and liver, the prodrug on entering the blood will be hydrolyzed very rapidly.

THIS PAPER deals primarily with the preparation and *in vitro* hydrolysis characteristics of a new prodrug (1, 2) form of acetaminophen and trichloroethanol possessing the following structure:



4-Acetamidophenyl 2,2,2-Trichloroethyl Carbonate (ATC)

Albert (3) has used the term "prodrug" to describe compounds which undergo biotransformation prior to exhibiting their pharmacologic effects. Harper (4) has used the term "drug latentiation" to describe chemical modification of a biologically active compound to form a new compound which upon *in vitro* enzymatic attack will liberate the parent compound.

During the past few decades there have been numerous *in vitro* studies describing hydrolysis of esters using serum and other body tissues as enzyme sources. Glick (5) measured the enzymatic hydrolysis of a variety of esters including those of choline. Related studies were undertaken by Adams and Whittaker (6) and Alles and Hawes (7). Levine and Clark (8) studied the relationship between structure and *in vitro* hydrolysis of various esters and amides in human serum. Frazer (9) performed hydrolysis studies on succinylcholine esters using cholinesterases. Other studies of these types have been reported

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in the literature as, for example, those of Kalow (10) and Casida and Augustinsson (11).

The carbonate ester, ATC, was designed to exhibit analgesic and sedative properties only after biotransformation following ingestion. Combining the sedative and analgesic activities of the parent drugs, acetaminophen and trichloroethanol, into a single molecule seemed logical since their pharmacologic activities are complementary, and their molar doses are somewhat equivalent. But the primary objectives were to impart new physical-chemical properties to the prodrug so that its absorption rate might be slowed, its dose-time-action profile modified in a useful way, and its profile of physical-chemical properties would be more desirable.

Both acetaminophen and trichloroethanol have an unpleasant taste, and trichloroethanol, a liquid, is especially unsuited for convenient pharmaceutical formulation. It was surmised that blocking the hydroxy groups through a carbonate bridge and linking the molecules together would suppress hydrophilic properties, improve taste, and yield a chemically neutral solid with more lipophilic quality than its parent drugs. Implicitly in the work underlying the preparation of ATC was the assumption that the compound would undergo cleavage in the body releasing the parent drugs at a rate that would result in a useful therapeutic action.

When administered to mice, ATC was shown to possess low acute oral toxicity, to be analgesic, and to reduce spontaneous motor activity, suggesting that it acted in a manner that would be expected of a prodrug of acetaminophen and trichloroethanol (1). Since the pharmaceutic and pharmacologic profiles of this compound seemed to have possible practical value in therapeutics, the authors set out to determine: (*a*) its hydrolysis rate in buffered water, (*b*) its cleavage rates in gastric and intestinal fluids, and (*c*) its cleavage rates in blood and tissue homogenates. It was hoped that these data would yield information about the hydrolytic stability of ATC in dosage forms, the importance and distribution of enzymes in the body that would cause it to be cleaved hydrolytically, the influence of enzymes on the cleavage rates of this apparent prodrug, and the cleavage, if any, of the compound in the gastrointestinal tract before absorption into the blood stream.

EXPERIMENTAL

Hydrolysis Studies

Chromatographic Procedure—The hydrolyses were carried out in a beaker with stirring at 37° as follows: 110 ml. of the biologic material (human gastric fluid or rat liver homogenate, *etc.*) was placed in the beaker and stirred until its temperature reached 37°. A 10-ml. blank sample of the biologic material was withdrawn. Three milligrams of ATC dissolved in 1 ml. of 95% ethanol was added to the biologic material and samples were withdrawn for analysis at appropriate time intervals.

Analyses were carried out as follows: samples (usually 10 ml.) removed from the reaction mixture were placed immediately in glass mortars containing three drops of concentrated hydrochloric acid (sufficient to bring the pH below 1). One gram of diatomaceous earth[1] for each ml. of reaction mixture plus 1 Gm. excess was added to each mortar, and this was triturated. This material was then packed on chromatography columns containing 5 Gm. of diatomaceous earth wet with 4 ml. of water. The mortars were "rinsed" with 2 Gm. of diatomaceous earth wet with 1 ml. of water, and this material was packed onto the columns. The columns were capped with a pledget of glass wool, and 50 ml. of reagent chloroform was poured in. The first 25 ml. of eluate was evaporated to dryness in a jet of air on a steam bath, and the residue was dissolved in 95% ethanol with gentle heating. The ethanol solution was transferred to a volumetric flask, brought to 25 ml. with ethanol, and analyzed spectrophotometrically using the absorption maximum of ATC at 240 mμ. The blank sample of the enzyme preparation was treated in exactly the same way, and the resulting alcohol solution was used in the reference cell of the spectrophotometer.

Initial experiments with mixtures of ATC and acetaminophen showed that the chromatographic procedure separated these two compounds completely.

Spectrophotometric Procedure—Hydrolysis reactions utilizing biologic materials as enzyme sources which were sufficiently dilute to allow direct UV analysis were carried out in the thermostated cell compartment of a Cary model 15 spectrophotometer. The biologic material (50 ml.) was warmed to 37° in a 125-ml. conical flask and a portion placed in the spectrophotometer reference cell. One-half milliliter of 95% ethanol containing 1.5 mg. of ATC was injected by means of a hypodermic syringe, and the flask was swirled gently until mixing was complete. A portion of this mixture was transferred to the sample cell of the spectrophotometer and the absorbances at 240 mμ (for ATC) or 300 mμ (for acetaminophen) were followed with time. The reaction was allowed to proceed until no further change in absorbance was observable, and the data were plotted in terms of Δ absorbance *versus* time (12).

At pH 7.4 the spectra of ATC and acetaminophen are similar; but there are sufficient differences in their molar absorptivities at 240 and 300 mμ to readily follow the hydrolysis reactions at either of these wavelengths. Since the hydrolysis reactions all followed first-order kinetics, plots of absorbance *versus* time, as the absorbance of the reaction mixture approached an equilibrium value, yielded the first-order rate constant. The values of many of the rate constants were verified by following the reactions at both wavelengths and, in several cases, by following the reactions using the chromatographic procedure. The same half-lives were obtained by all three techniques.

[1] Celite, Johns-Manville Corp., New York, N. Y.

Syntheses

2,2,2-Trichloroethyl Chloroformate (13)—Conversion of trichloroethanol to the chloroformate was done in a hood. Vapors of phosgene and the chloroformate[2] were trapped in a sodium hydroxide solution.

A mixture of 150 ml. of toluene and 41 ml. (0.5 mole) of pyridine was cooled wih a dry ice–isopropanol bath. Phosgene (0.75 mole) was added with stirring to this cold mixture. Freshly distilled trichloroethanol (0.5 mole) was then dripped into the mixture, and the dry ice–isopropanol bath was removed after 10 min. The mixture was then stirred for 1 hr. with ice water cooling and for 4 hr. at room temperature. The excess phosgene was removed *in vacuo* at room temperature and the pyridine hydrochloride was removed by filtration.

4-Acetamidophenyl 2,2,2-Trichloroethyl Carbonate—The reaction between acetaminophen and 2,2,2-trichloroethyl chloroformate was carried out in a hood.

Seventy-five and one-half grams (0.5 mole) of 4-hydroxyacetanilide was dissolved in a solution of 20 Gm. (0.5 mole) of sodium hydroxide in 300 ml. of water. This solution was dripped into a chilled toluene solution of the above chloroformate with stirring over a period of 15 min., and stirring was continued for 90 min. The precipitate was recrystallized from dilute alcohol (charcoal) to give 107 Gm. (66%) of product, a white crystalline solid, m.p. 151–153.5°.

Anal.—Calcd. for $C_{11}H_{10}Cl_3NO_4$: C, 40.46; H, 3.09; Cl, 32.57. Found: C, 40.67; H, 3.14; Cl, 32.47.

ATC has a solubility in water of about 35 mcg./ml., and in cyclohexane of 56 mcg./ml., at 37°. It is much more soluble (> 1%) in alcohol and chloroform. As a fine powder, ATC is poorly wetted by water and tends to float.

Materials

Phosphate Buffer—A 0.02 *M* phosphate buffer solution was used to study hydrolysis rates of ATC in water at various pH's. A 0.1 *M*, pH 7.4 phosphate buffer was used in hydrolysis studies involving biological materials, with the exception of human gastric fluid. All hydrolysis studies were done at about body temperature, 37°.

Human Gastric and Intestinal Fluids—These materials were obtained from patients at the Presbyterian University of Pennsylvania Medical Center, Philadelphia. The gastric fluid had a pH of 1.1 and was used undiluted in the hydrolysis studies. The intestinal fluid was used for hydrolysis studies in dilutions of 1, 2, 3, and 4% in phosphate buffer, pH 7.4. The hydrolysis studies in gastric fluid were carried out using the chromatographic procedure, whereas the studies in intestinal fluid employed the spectrophotometric procedure.

Human Plasma—Samples of human plasma were obtained from the Philadelphia Serum Exchange, Children's Hospital. Studies utilizing fresh plasma, 1 part in 50 of phosphate buffer, were carried out using the spectrophotometric procedure to follow hydrolysis rates.

Rat Plasma—The plasma was separated from fresh blood collected in a heparinized beaker by centrifuging the blood at about 20,000 r.p.m. for 5 min.; then the plasma was frozen immediately and stored frozen until used. Hydrolysis studies were carried out utilizing rat plasma at a concentration of 1% in phosphate buffer. The spectrophotometric method was used to follow concentrations of ATC or acetaminophen.

Rat Liver—A Dierolf rat (about 200 Gm.) was killed, and its liver was removed, weighed, and homogenized in a small volume of ice cold normal saline solution using a Waring blender. The homogenate was strained through cotton gauze and brought to 100 ml. with cold normal saline solution. This suspension was then diluted with sufficient phosphate buffer to make a final concentration of 0.1% liver tissue based on the wet weight of the original liver. Hydrolysis studies in this suspension were carried out using the chromatographic procedure.

Rat Intestinal Mucosa—A Dierolf rat (about 200 Gm.) was killed, and its entire small intestine [about 61 cm. (24 in.)] was removed. The intestine was opened, and the solid contents were removed by gentle rinsing with cold water. Mucosal scrapings from the entire segment were obtained by means of a microspatula with a curved blade. The scrapings were mixed with cold normal saline solution (10 ml.) in a tissue grinder, and the resulting suspension was filtered through filter paper. The filtrate was diluted 1:20 (volumetrically) with phosphate buffer, and hydrolysis rate studies were carried out in this solution using the spectrophotometric procedure.

RESULTS AND DISCUSSION

Nonenzymatic Cleavage of ATC—The influence of pH on the hydrolysis rates of this compound was studied: (*a*) to determine to what extent this might influence shelf life of dosage forms prepared from it, and (*b*) to estimate if these rates alone would be sufficiently fast to produce drug from prodrug at a rate which would elicit a pharmacologic response.

In Fig. 1 there are plotted the half-lives ($t_{1/2}$) of ATC as a function of pH in the pH range 2 to 10.5. Hydrolysis reactions all followed first-order kinetics. Studies on the effect of phosphate ion, though not reported here, were done to determine how this might influence the hydrolysis rate. Some catalysis due to phosphate was observed at pH's above 8. However, 0.02 *M* phosphate buffer exerted almost no effect on the hydrolysis rate in this pH range. Below pH 8, phosphate buffer exerted virtually no catalytic effect on hydrolysis.

Between pH 7.6 and 10.5 the plot of log $t_{1/2}$ *versus* pH (Fig. 1) is a straight line with a slope of approximately −1, indicating that the hydrolytic process is first-order with respect to hydroxyl ion in this pH range. Below pH 7, the hydrolytic rate approaches a constant value perhaps due to simple water hydrolysis. At 7.4, the pH of blood and other tissue fluids, the $t_{1/2}$ is about 7 hr. At pH's of 1 to 3, corresponding to stomach pH, the $t_{1/2}$ is about 15 hr. Therefore, at pH's normally encountered in the body, *i.e.*, about 1 to 7.4, it is apparent that the $t_{1/2}$ in the absence of enzymes is always more than about 7 hr. From these data we surmise that at the pH's of body fluids the cleavage of this compound would

[2] Vapors of the chloroformate are very irritating, and they are reported to be as toxic as chlorine (14).

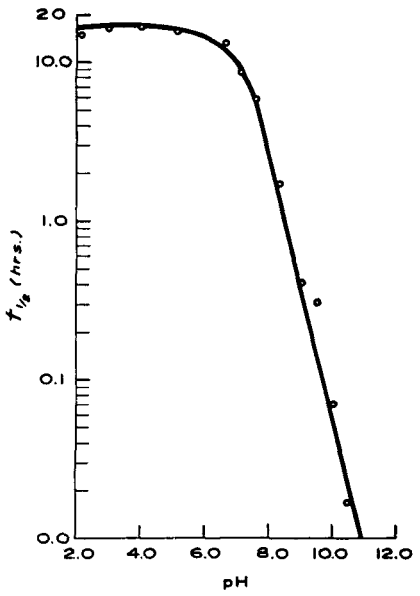

Fig. 1—Plot showing half-lives at various pH's for hydrolysis of 4-acetamidophenyl 2,2,2-trichloroethyl carbonate (ATC) in 0.02 M phosphate buffer at 37°.

not occur at a sufficient rate in the body to elicit a useful response from the acetaminophen and trichloroethanol that were formed unless the hydrolysis reaction was catalyzed by enzymes.

Hydrolysis of ATC Catalyzed by Enzymes from Human and Animal Materials—Since preliminary pharmacologic and biochemical studies, to be reported in another paper, indicated that ATC was an active compound with the predicted pharmacologic properties, knowledge pertaining to sites in the body where the presence of enzymes might induce cleavage of the compound took on added significance.

Thus, it became of interest to assess the hydrolytic effects of various body fluids and tissues, for example, gastrointestinal fluids, blood, and liver. These studies were concerned primarily with the enzymic cleavage rate of the compound relative to its cleavage rate in buffer. No attempts were made to elucidate the mechanism of the enzyme-induced cleavage of ATC, nor to identify the specific enzymes responsible for this cleavage.

All the reactions studied followed, or were assumed to follow, first-order kinetics; and all the data were plotted as log Δ absorbance *versus* time from which the half-lives were determined. Occasionally, it was either impossible or impractical to allow a reaction to go to completion in order to determine the terminal absorbance of the reaction mixture, and, occasionally, apparent terminal absorbance values observed experimentally produced curved semilog plots. In these cases, the terminal absorbances were adjusted to straighten the semilog plots. This approach was found to be as reliable and somewhat more convenient than the Guggenheim method of plotting first-order data (12).

Although enzyme reactions often are not simple first-order reactions, the half-lives determined in these experiments are indicative that the enzyme systems we studied have a definite catalytic effect on the hydrolysis of ATC and that enzyme systems obtained from human and animal sources vary widely in their ability to accelerate the hydrolysis reaction.

In cases of enzyme catalyzed reactions, it is often observed that the rate of decrease of substrate concentration, $-dS/dt$ varies with the substrate concentration [S] according to the Michaelis-Menten equation,

$$\frac{-dS}{dt} = \frac{V[S]}{K_S + [S]}$$

where V is the maximum velocity reached at infinite concentrations of substrate, and K_S is the dissociation constant of the enzyme-substrate complex. When $[S] \ll K_S$, the velocity of the reaction is proportional to the substrate concentration, *i.e.*, the reaction follows first-order kinetics. Thus, in enzyme-catalyzed hydrolysis reactions, pseudo first-order kinetics are often observed through a significant portion of the reaction.

In our studies of ATC hydrolysis using body fluids and tissues as enzyme sources, first-order kinetics were observed usually beyond 50% hydrolysis of the substrate. Thus, in these screening studies it was convenient to determine approximate first-order hydrolysis rate constants. Enzyme-catalyzed hydrolyses, therefore, are expressed as half-lives or in terms of the quotient

$$\frac{t_{1/2}\text{ (water)}}{t_{1/2}\text{ (biologic material)}}$$

at pH 7.4 and 37°.

Hydrolysis of ATC in Human Gastric Fluid—Half-life values in human gastric fluid were in excess of 5 hr. indicating that if there were enzymes here that could catalyze the hydrolysis reaction their effects were insignificant.

Hydrolysis of ATC in Human Intestinal Fluid (HIF)—Typical rates of hydrolysis of ATC in human intestinal fluid, diluted with 0.1 *M* phosphate buffer, pH 7.4, are summarized in Table I.

These results support the view that the fluids of the lumen of the intestine possess substances which have rather pronounced catalytic effects on the hydrolysis of ATC. For example, measured in 4% human intestinal fluid, the hydrolysis rate proceeds 18 times faster than in buffer alone. Though ATC might dissolve and be absorbed intact to some extent from the stomach, it appears that some hydrolysis must occur in the fluids of the intestinal lumen prior to absorption. Therefore, both ATC and its cleavage products could be absorbed from the small intestine.

Effect of Mucosal Scrapings from Rat Small Intestine on ATC Cleavage—Mucosal scrapings appear to be high in esterases that cleave ATC. When ATC

TABLE I—EFFECT OF HUMAN INTESTINAL FLUID ON CLEAVAGE RATES OF ATC AT 37°

Concentration of Human Intestinal Fluid (HIF) in 0.1 *M* Phosphate Buffer, pH 7.4, %	$t_{1/2}$, Min.	$t_{1/2}$ (buffer)/ $t_{1/2}$ (HIF in buffer)
0	420	1
1	98	4
2	46	9
3	33	13
4	23	18

was dissolved to a concentration of 30 mcg./ml. in 200 ml. of phosphate buffer containing the mucosal scrapings of the entire small intestine of a rat, it underwent hydrolysis with a half-life of 5.5 min. This is about 65 times the hydrolysis rate observed in buffer alone. These data support the hypothesis that a drug such as ATC might undergo considerable hydrolytic cleavage in the process of passing through the mucosal lining as it is being absorbed in the intestine.

Hydrolysis by Rat Liver—When ATC was dissolved to a concentration of 30 mcg./ml. in a 0.1% suspension of rat liver in phosphate buffer, it hydrolyzed with a half-life of 5 min. This is about 70 times as fast as the hydrolysis in buffer alone.

Hydrolysis in Plasma—A dilution of 1:50 human plasma in phosphate buffer caused a 30 mcg./ml. solution of ATC to cleave with a half-life of 20 min. This is about 18 times faster than the hydrolysis rate in buffer; on the other hand, it is a much slower rate than was observed in rat plasma of the same dilution. Figure 2, depicting hydrolysis in diluted human plasma, represents typical data observed in the catalyzed hydrolysis of ATC in the presence of body fluids and tissues.

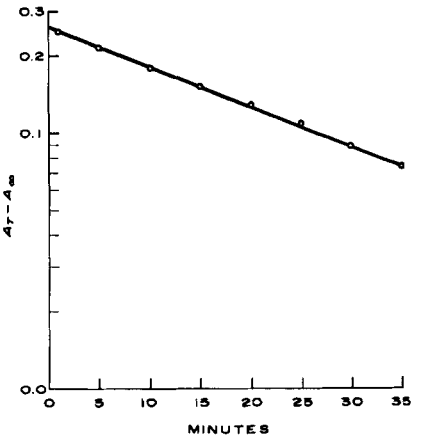

Fig. 2—First-order plot of the hydrolysis of 4-acetamidophenyl 2,2,2-trichloroethyl carbonate (ATC) in pH 7.4 phosphate buffer (0.1 M) containing 2% (v/v) human plasma at 37°. Absorbances were determined at 240 mμ. A_t, absorbance at time t; A_∞, absorbance when reaction is apparently complete; half-life, about 20 min.

CONCLUSIONS

These studies have shown the utility of the carbonate linkage in creating a prodrug from two well-known drugs. They show how the physical-chemical properties of both acetaminophen and trichloroethanol were modified substantially to produce a new compound with good lipid solubility but with low water solubility and a relatively slow dissolution rate. The compound is virtually tasteless apparently as a result of "locking" the hydrophilic hydroxy groups of the parent drugs and markedly decreasing the aqueous solubility of the parent drugs. The profile of new physical properties makes it possible to use ATC in certain dosage forms, such as tablets, which would have been impossible with a simple physical combination of the parent drugs.

A hydrolysis rate corresponding to a half-life of 15 hr. in water at pH 4–7 suggests that suspensions of ATC in water would not be stable for prolonged periods despite its very low aqueous solubility. On the other hand, the low water solubility, coupled with a dose that would be relatively large, suggest that suspensions might be prepared that would retain appreciable potency, at least for several weeks.

A hydrolysis rate at pH 2 corresponding to a $t_{1/2}$ of 15 hr. coupled with an intrinsic low water solubility and slow cleavage rate in human gastric fluids suggest that this compound, when administered orally, is absorbed from the stomach primarily in the form of ATC. The presence in human intestinal fluid and rat intestinal mucosa of enzymes which catalyze the cleavage of ATC suggest that absorption from the intestine of both ATC and its cleavage products could occur simultaneously. The fact that esterases are abundant in the plasma and liver would suggest that in animals and humans the ATC that was absorbed intact would be very short lived and might not even be detectable in the blood but rather, would be quickly converted to acetaminophen and trichloroethanol.

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Keyphrases

4-Acetamidophenyl 2,2,2-trichloroethyl carbonate (ATC)—synthesis
Prodrug—acetaminophen, trichloroethyl carbonate ester
Hydrolysis, ATC—pH, enzyme effect
Column chromatography—separation
UV spectrophotometry—analysis