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O-Acylsalicylamides as possible prodrugs for salicylamide I. Kinetics and mechanisms of their degradation and reaction with enzymes and sodium bisulfite

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Summary

Three prodrugs of salicylamide, O-acetylsalicylamide (I), O-acetylsalicylsalicylamide (II), and O-glutarylsalicylamide (III) were prepared and their rates of degradation were studied over a wide pH range. These compounds were found to undergo O → N acyl transfer to the corresponding imide even in acidic environments. This reaction was followed spectrophotometrically at 355 nm.

The effect of horse serum esterases on the hydrolysis of compounds I and III was also studied. In the presence of esterases and human plasma, the above prodrugs were found to cleave exclusively to salicylamide and not to the imide.

In the presence of sodium bisulfite, the prodrugs I and III were found to undergo two parallel reactions and resulted in the formation of the imide and salicylamide.

Introduction

Salicylamide, a widely used analgesic and antipyretic drug, has an advantage over aspirin and salicylate because it lacks their undesirable side-effects of gastric irritation and bleeding. The drug, however, is extensively conjugated to sulfate and glucuronide in the gastrointestinal tracts of animal and man during the absorption process and by first-pass metabolism (Guglar et al., 1976; Alam et al., 1977; Barr

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and Riegelman, 1970). Because of that, the drug must be used in large doses to obtain a detectable plasma level of the free drug (Riegelman et al., 1973). Since the drug is conjugated in the phenolic group, transient protection of this group via acylation may minimize its metabolism in the gastrointestinal tract and may increase its bioavailability.

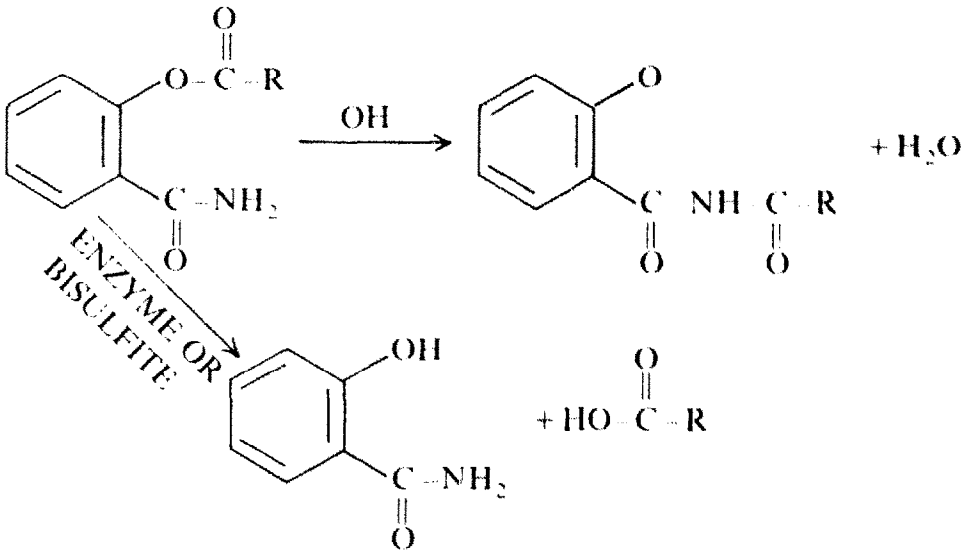
For any ester of salicylamide to be useful as a prodrug, it must meet the following criteria: (a) it must be stable in the gastrointestinal tract prior to absorption; (b) it must be rapidly and completely absorbed; and (c) it must revert enzymatically or otherwise to salicylamide after absorption.

In order to examine whether certain esters meet the above criteria, O-acetylsalicylamide (I), O-acetylsalicylsalicylamide (II) and O-glutarylsalicylamide (III) were synthesized and tested for their stability and for their in vitro enzymatic rates of conversion to salicylamide.

Although O-acetylsalicylamide is known to undergo O → N acetyl transfer in neutral and alkaline solutions (Behme et al., 1964), the rate of this reaction was not studied at pH values below pH 7. Since salicylamide itself is very lipophilic and is known to be absorbed rapidly from the stomach and the upper part of the intestine where the pH ranges from 2 to 5 (Barr et al., 1970; Bates et al., 1969), it was felt that information on the stability of these esters over a wide pH range and especially in more acidic environment is needed before their bioavailability is determined.

The purpose of this study is: (1) to examine the rate of O → N acyl transfer of I, II and III over the pH range of 3–9; and (2) to determine their rate of conversion to salicylamide in the presence of horse serum esterases and human plasma.

To obtain an insight into the mechanism and the magnitude of the above reactions, the reaction between the prodrugs and bisulfite was examined as a function of pH and bisulfite concentration. Sodium bisulfite was chosen as a model nucleophile since it has been shown that it has a pronounced catalytic effect on the hydrolysis of phenolic esters such as aspirin (Munson et al., 1977) and since bisulfite



Scheme I

is a common antioxidant in many pharmaceutical products.

The results of this study strongly suggest that in the absence of enzymes, these esters undergo O → N transacylation to the corresponding imides even in acidic environments; whereas, in the presence of horse serum esterases or human plasma, these esters cleave exclusively and rapidly to salicylamide (Scheme I).
In the presence of sodium bisulfite, however, these esters undergo parallel reactions to form the imide and salicylamide. The results also suggest that the rate of imide formation was not catalyzed by bisulfite, whereas the rate of salicylamide formation was dependent on bisulfite concentration as well as on the pH.

Materials and methods

Materials

The following chemicals were used in this study; salicylamide, glutaric anhydride, acetylsalicyloyl chloride and sodium bisulfite (Aldrich), acetyl chloride (Fisher) and horse serum esterases (17.6 units/mg) (Sigma). Human plasma was obtained from donors. The instruments used in this study were an NMR spectrophotometer, a recording spectrophotometer (Varian Cary 15) and IR spectrophotometer (Perkin-Elmer 567).

Synthesis of the esters of salicylamide

O-Acetylsalicylamide was synthesized according to the procedure described by McConnan et al. (1906). The melting point was found to be 153–154°C. The elemental analysis was calculated for $C_9H_9O_3N$: C, 60.33; H, 5.06; N, 7.82; Found C, 60.61, H, 5.1, N, 7.93.

The acetylsalicyl salicylamide was synthesized as follows. 27.5 g of salicylamide were dissolved in 55 ml of freshly distilled pyridine with constant stirring; the solution was cooled down in a dry-ice–acetone mixture to approximately −15°C. The mixture was then removed from the dry-ice–acetone bath. As a second phase, 40 g of O-acetylsalicyloyl chloride were dissolved in 50 ml of ethylacetate, and the resulting solution was added in a drop-wise fashion to the solution of salicylamide in pyridine with constant stirring. The temperatue was kept at approximately −15°C during the course of addition. After the addition of O-acetylsalicyloyl chloride, the reaction mixture was stirred for an additional 30 min at −15°C during which time a white gelatinous material was formed. At the end of the 30 min period, 150 ml of pentane was added and the stirring was continued for 10 min.

The gelatinous material was then separated from the reaction mixture by filtration and washed several times with additional amounts of pentane. The material was dissolved in methanol and the methanolic solution was added to 500 ml of 1 N ice-cold sulfuric acid with continuous stirring. A precipitate was formed immediately and was stirred for 10 min. The solid material was filtered, washed several times with cold distilled water and then air-dried. The dried material was recrystallized several times from pentane–ethylacetate–benzene mixture (5 : 10 : 5) to give an amorphous powder which melted at 163°C with decomposition.

The structure of the compound was confirmed by elemental analysis and by NMR. Analytical calculation for $C_{16}H_{13}O_5N$: C, 64.15; H, 4.34, N, 4.67. Found: C, 64.15; H, 4.8; N, 4.92. NMR ($CDCl_3$): δ2.3 (s, 3, $-C\underline{H}_3$), δ7–8.3 (m, 10, aromatic and $-N\underline{H}_2$).

Glutarylsalicylamide was prepared from sodium salicylamide and glutaric anhydride according to the following procedure. To a suspension of 20 g (0.12 M) of sodium salicylamide in ether–benzene mixture (50/50 v/v) was added a solution containing 13.7 g (0.12 M) glutaric anhydride in an ether–benzene mixture in a drop-wise fashion over a period of about 45 min with constant stirring. Once the addition was completed, the stirring was continued for a period ranging from 120 to 150 h at room temperature. At the end of the period the precipitate was isolated by filtration, washed several times with an ether–benzene mixture and then petroleum ether and air-dried. The dry material was added to 400 ml of 1 N ice-cold sulfuric acid, and stirred for 10 min to liberate the free hemi-ester. The precipitate was then filtered, washed several times with cold water, and dried under vacuum. The dried material was recrystallized from ether–benzene mixture and then from benzene–dioxane (2:3) to give a white crystalline material which melted at 152°C with decomposition. Analytical calculation for $C_{12}H_{13}O$: C, 57.37; H, 5.21; N, 5.57. Found: C, 57.95; H, 5.62; N, 5.93. The structure was further confirmed by C^{13}NMR.

Rate of formation of N-acylsalicylamides from O-acylsalicylamides

All of the measurements were carried out at 25°C. In a typical run, a stock solution of the prodrug (1×10^{-3} mol/l) to be studied was freshly prepared in spectral grade dioxane. 100 μl of this solution were placed in a 1 cm path-length spectrophotometer cell and exactly 3 ml of the desired buffer at the desired pH and ionic strength were added to the cell. The cell was then quickly inverted several times to ensure uniform mixing, and the increase in the absorbance (A) was observed at 355 nm as a function of time. The observed first-order rate constants were obtained by linear regression analysis of $\log(A_\infty - A_t) = kt/2.303 + b$, using a Wang Model 600 (program number 2003).

The effect of pH on the rate of formation of N-acylsalicylamide was determined. The solutions were maintained at the desired pH using acetate (pH 3–5.5) and phosphate (pH 6–9) buffers. Ionic strength was adjusted to a value of 1.0 using sodium chloride. All the kinetic studies were carried out at constant temperature.

Effects of buffer concentration on the rate of formation of N-acetylsalicylamide and N-glutarylsalicylamide was studied at pH 6 and 8, using phosphate 0.05–0.8 M buffers, while maintaining constant ionic strength, using sodium chloride. Ionic strength effects on the rate of reaction were also investigated. The ionic strength was adjusted to the desired value using sodium chloride.

In addition to the spectrophotometric determination, the reaction mixture was analyzed using HPLC according to a procedure previously described (Gautam et al., 1981).

Enzymatic hydrolysis

All of the measurements were conducted at 37°C in an aqueous 0.01 M, pH 7.4,

phosphate buffer. The enzyme solution of the required activity was prepared by dissolving the required amount of the enzyme powder in a sufficient amount of the buffer. The solution was equilibrated at 37°C for 30 min. A stock solution of the prodrug to be studied was prepared to contain 0.5 mg of the drug/ml of absolute ethyl alcohol.

In a typical run, 100 μl of the prodrug in ethanol were placed in a 1 cm path-length spectrophotometer cell and then 3 ml of the enzyme solution was injected directly into the cell (while the cell was in the compartment) using a syringe. The increase in the absorbance at 302 nm was followed against a reference solution containing the same concentration of the enzyme in the buffer.

For the human plasma study, plasma was obtained by centrifugation of fresh blood and 5 ml plasma sample was collected and equilibrated at 37°C for 30 min. For this study, a stock solution of the prodrug was prepared to contain 3 mg of the compound in 1 ml of absolute ethyl alcohol. 100 μl of the prodrug solution was added to 1 ml of the plasma at 37°C. 100 μl of the reaction mixture were withdrawn periodically and 3 ml of 0.01 M, pH 4.5, acetate buffer was added to quench the reaction and the presence of salicylamide in the solution was determined spectrophotometrically at 302 nm against a blank plasma solution which was treated in the same manner.

In order to confirm the presence of salicylamide in the reaction mixture, both the enzyme solutions and the plasma solutions were analyzed by high-pressure liquid chromatography according to the previously reported procedure (Gautam et al., 1981).

Reaction with sodium bisulfite

The rates of reaction with sodium bisulfite were determined at 35 ± 0.05°C. Sodium bisulfite solutions were prepared freshly for each run using doubly distilled water that was saturated with nitrogen for at least 2 h. The ionic strength of the solutions was adjusted to a value of 1.0 using sodium chloride and the pH was adjusted to the desired value using sodium hydroxide solution.

Stock solutions of the prodrugs were prepared to contain 1×10^{-2} mol/l of the compounds in spectral grade dioxane. 100 μl of the dioxane solution was placed in a 1 cm path-length spectrophotometer cell and exactly 3 ml of the bisulfite solution were added to the cell. The cell was then quickly inverted several times to ensure uniform mixing and the increase in absorbance at 302 nm for the formation of salicylamide or at 355 nm for the formation of the imide was followed as a function of time until no further change was observed. For every experiment at every bisulfite solution, the reference cell contained the corresponding bisulfite solution.

The observed first-order rate constants were calculated from the slope of straight lines obtained by plotting the $\log(A_\infty - A_t)$ versus time.

Results and discussion

Degradation in aqueous solution

The formation of salicylamide from O-acylsalicylamides was found to be negligi-

ble in aqueous solutions in the pH range 3–9. However, these compounds were found to undergo an O → N acyl transfer at surprisingly rapid rates even in acidic solutions. This was confirmed by spectral changes and HPLC. When aqueous buffer solutions were added to a dioxane solution of these compounds, a peak was observed at a wavelength of 355 nm and not at 302 nm where salicylamide has its maximum absorbance. The absence of salicylamide was further confirmed by a specific HPLC method (Gautam et al., 1981). The rate of formation of N-acylsalicylamides was found to be first-order with respect to the compounds, independent of buffer concentration and ionic strength and dependent on pH. For compounds I and II, plots of log K_{obs}, the observed first-order rate constants versus pH gave straight lines whose slopes were one, suggesting that the rate of reaction had a first-order dependence on hydroxyl ion concentration.

The standard logarithmic rate (Eqn. 1) was found to be consistent with the results

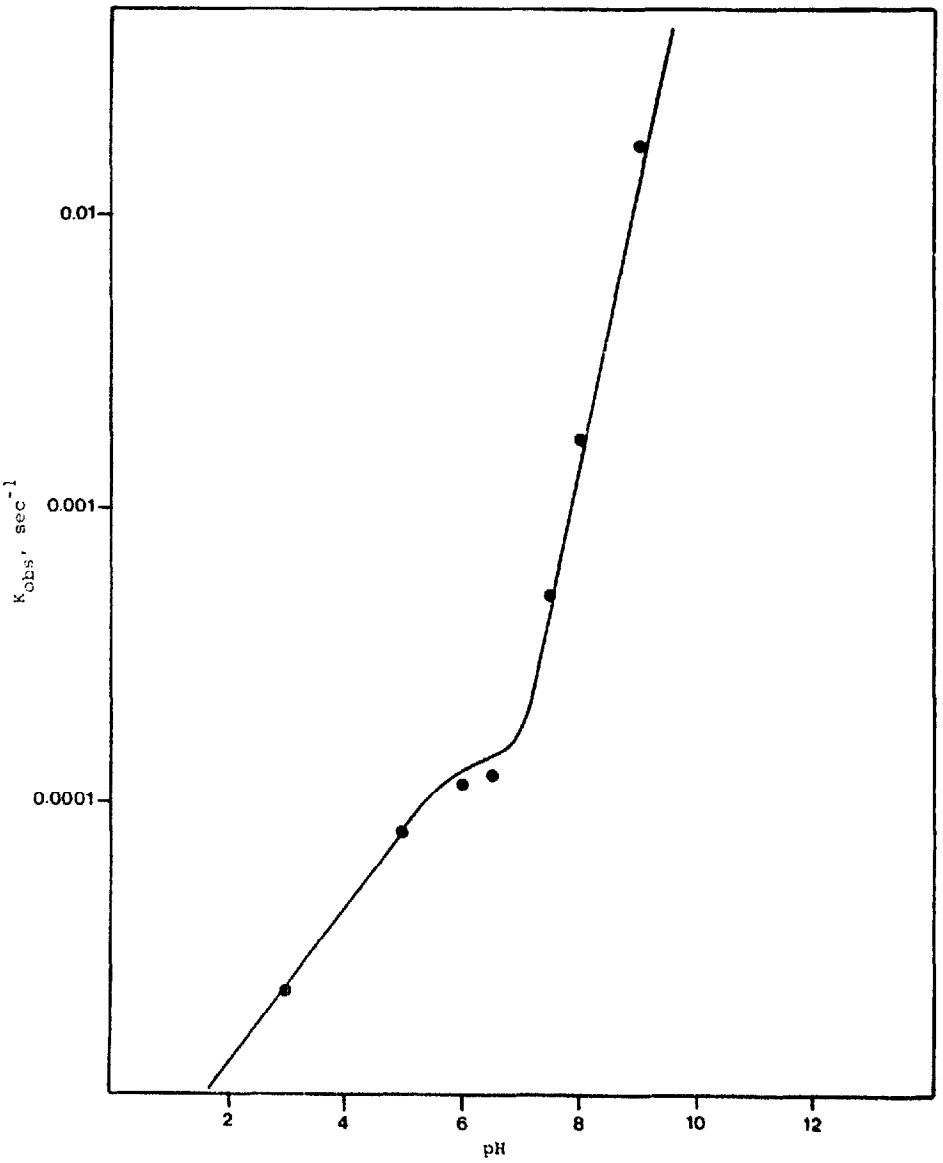


Fig. 1. The pH–rate profile for the degradation of compound III at 25°C.

obtained for compounds I and II

$$\log K_{obs} = \log k_{OH^-} + \log k_w + pH \quad (1)$$

where k_{OH^-} is the second-order rate constant for hydroxyl ion catalysis. The values of k_{OH^-} for compounds I and II were calculated to be 1.4×10^4 and 0.78×10^4 $l \cdot mol^{-1} \cdot s^{-1}$, respectively.

In the case of O-glutarylsalicylamide, however, a plot of log k_{obs} versus pH did not result in a straight line (Fig. 1); thus Eqn. 1 is not applicable. Since the compound can exist in solution in both ionized and unionized forms, a rate equation consistent with the data is shown below:

$$-\frac{d(prodrug)}{dt} = \frac{d(imide)}{dt} = k_{1_{OH^-}}(OH^-)[prodrug] + k_{2_{OH^-}}(OH^-)(prodrug^-)$$

$$= k_{obs}(prodrug)_{total} \quad (2)$$

where $k_{1_{OH^-}}$ and $k_{2_{OH^-}}$ are the second-order rate constants for hydroxyl ion attack of the unionized and the ionized forms of the drug, respectively.

$$\text{Since } (prodrug)_{total} = (prodrug) + (prodrug^-) \quad (3)$$

and

$$K_a = \left[\frac{(prodrug^-)(H^+)}{(prodrug)}\right] = 4.58 \times 10^{-5} \quad (4)$$

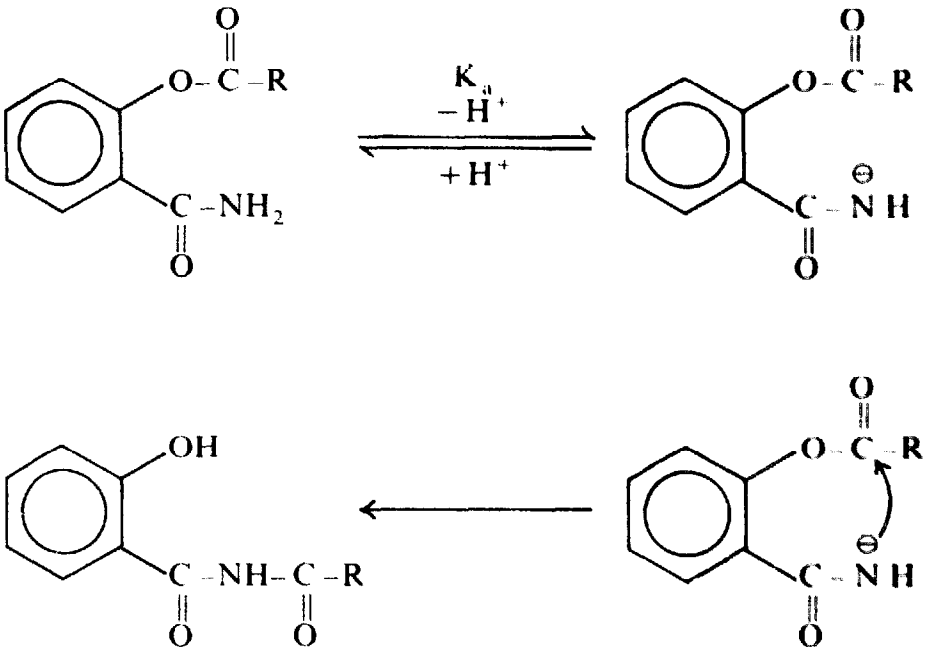
where K_a is the ionization constant for the free carboxyl group. Substituting for the species involved using Eqns. 2, 3 and 4 results in Eqn. 5.

$$k_{obs} = k_{1_{OH^-}}\left(\frac{[OH^-][H^+]}{(H^+) + K_a}\right) + k_{2_{OH^-}}(OH^-)\left(\frac{K_a}{(H^+) + K_a}\right) \quad (5)$$

The line in Fig. 1 was obtained by calculating the theoretical line from Eqn. 5 using values of k_{obs} at the two extremes of the pH–rate profile. The points are experimental values. As seen from the data of Fig. 1, the fit between the calculated values and those determined experimentally is close. The second-order rate constants $k_{1_{OH^-}}$ and $k_{2_{OH^-}}$ were calculated to be 3.6×10^5 $l \cdot mol^{-1} \cdot s^{-1}$ and 1.7×10^3 $l \cdot mol^{-1} \cdot s^{-1}$, respectively.

The accepted mechanism for the O → N acyl transfer in compounds similar to the above and for compounds containing ureido functional group in an ortho position to an ester is shown in Scheme II (Behme et al., 1964; Hegarty et al., 1970; Stella et al., 1973).

The first step involves a rapid and reversible ionization of the amide nitrogen followed by a nucleophilic attack of the amide anion on the ester carbonyl group as the rate-determining step.

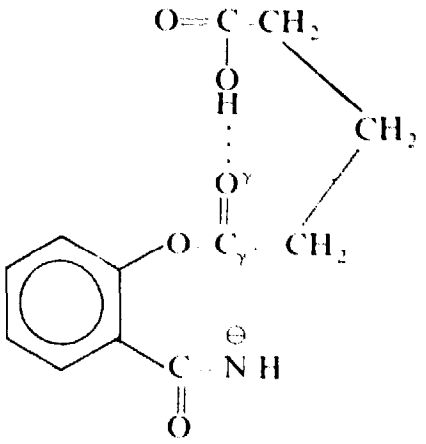


Scheme II

Using the above accepted mechanism as the basis for discussion, it can be seen that the nature of the acyl group can affect the rate of the reaction. For example, the second-order rate constant for compound II is half as fast as that observed for compound I. This can be easily explained as being based on steric hindrance. The sheer bulk of the O-acetylsalicyloyl group can account for the difference in the rates of hydrolysis of the two compounds.

In the case of O-glutarylsalicylamide, the second-order rate constant, $k_{1,III}$, calculated on the basis of the involvement of the protonated species of the acid was found to be 30 times greater than that calculated for I. The rate constant, $k_{2,III}$, which represents the involvement of the ionized carboxyl group is one order of magnitude slower than that calculated for I.

These data can be rationalized based on the involvement of the carboxyl group.



Scheme III

In the case of the free carboxyl group, the formation of a cyclic 8-membered intermediate through hydrogen bonding, Scheme III, is very possible. St. Pierre et al. (1968) postulated an 8-membered ring transition state for the aminolysis of aspirin. Such hydrogen bond formation will render the carbonyl group to be more positive and consequently more accessible to an attack by the amide anion. For the carboxylate species, such hydrogen bond formation is not possible. Furthermore, the negative charge carried by the carboxylate group will render, by virtue of electrostatic repulsion, an attack by the negatively charged amide more difficult. Consequently, the ionized species of III hydrolyzes slower than I.

Stella et al. (1973) found that the positively charged amine esters of hydantonic acid closes faster than the corresponding simple alkyl esters. These differences in the rate of reaction were rationalized based on the involvement of the positively charged amine in stabilizing the transition state.

The above data indicates that these esters degrade in aqueous solution as their corresponding imides and that the above reactions are influenced by the pH. At pH < 6, the O $\rightarrow$ N acyl transfer reaction is relatively slow.

Enzymatic hydrolysis

The enzymatic study was carried out on compounds I and III only. In the presence of horse serum esterases and human plasma, the compounds were found to cleave quantitatively to salicylamide. The formation of salicylamide was confirmed spectrophotometrically and by a specific HPLC method (Gautam et al., 1981). The ultraviolet absorption spectra of the reaction mixture exhibited a peak at 302 nm and not 355 nm. The absorption spectrum was superimposable on the UV spectra of

TABLE I

EFFECT OF ENZYME CONCENTRATION ON THE RATE OF SALICYLAMIDE FORMATION FROM O-ACETYLSALICYLAMIDE (T = 37°C)

Enzyme concentration (units/ml)	k_{obs} (s^{-1}) O-acetylsalicylamide
10	0.020
20	0.040
27.5	
30	0.054
40	0.075

EFFECT OF ENZYME CONCENTRATION ON THE RATE OF SALICYLAMIDE FORMATION FROM O-GLUTARYLSALICYLAMIDE (T = 37°C)

Enzyme concentration (units/ml)	k_{obs} (s^{-1}) O-glutarylsalicylamide
20	0.0021
27.5	0.0030
40	0.0040

salicylamide dissolved in the enzyme solution at the same pH.

The rate of formation of salicylamide at 302 nm was found to be first-order with respect to the prodrugs and dependent on the enzyme concentration. Table 1 shows the dependency of the observed first-order rate constants on the enzyme concentration. It is evident from these data that the rate of formation of salicylamide is directly proportional to the concentration of the enzyme. In the presence of human plasma, however, the reaction was too fast to follow,and quantitative formation of salicylamide was observed within the first 15 s after the addition of the plasma to the drug.

The above data also showed that at any given enzyme concentration, the O-glutarylsalicylamide is hydrolyzed at a much slower rate than O-acetylsalicylamide. This may be due to the fact that the negatively charged carboxylate group of the glutaryl derivative can inhibit the interaction between the substrate and the anionic site of the enzyme. It is known, for example, that benzoyl arginine ethyl ester in the presence of trypsin undergoes hydrolysis much faster than N-acetylglycine ethyl ester. Such differences in hydrolysis rate was attributed to the fact that benzoylarginine ethyl ester, a positively charged substrate, can interact with an anionic site of the enzyme, whereas acetylglycine ethyl ester, an uncharged substrate, cannot (Jencks, 1969). The above enzymatic data thus indicate that the enzymatic cleavage of the prodrugs to salicylamide is very fast in the human plasma and much faster than the O → N acyl transfer.

Reactivity of sodium bisulfite toward compounds I and III

When solutions of bisulfite at pH 7.4 were added to the prodrug solutions, two absorption peaks were observed, one at 355 nm which corresponds to the imide and one at 302 nm which corresponds to salicylamide peak. The presence of salicylamide was further confirmed by high-pressure liquid chromatography.

Furthermore, as bisulfite concentration increased, the ratio of salicylamide peak to the imide peak at equilibrium increased linearly ($r^2 = 1$). The above data strongly

TABLE 2

THE SECOND-ORDER RATE CONSTANT FOR SODIUM BISULFITE CATALYSIS AS CALCULATED[a] AT DIFFERENT pH VALUES (T = 35°C)

pH	O-Acetylsalicylamide ($k_{SO_3^{2-}} \times 10^2$ l·mol^{-1}·s^{-1})	O-Glutarylsalicylamide ($k_{SO_3^{2-}} \times 10^2$ l·mol^{-1}·s^{-1})
5.38	9.20	–
5.77	9.17	–
6.00	–	2.0
6.50	–	1.9
6.60	8.55	–
6.80	–	1.8
7.40	9.34	2.1[a]

[a] Calculated from two experiments at two different bisulfite concentrations using Eqn. 10 and data from Fig. 3.

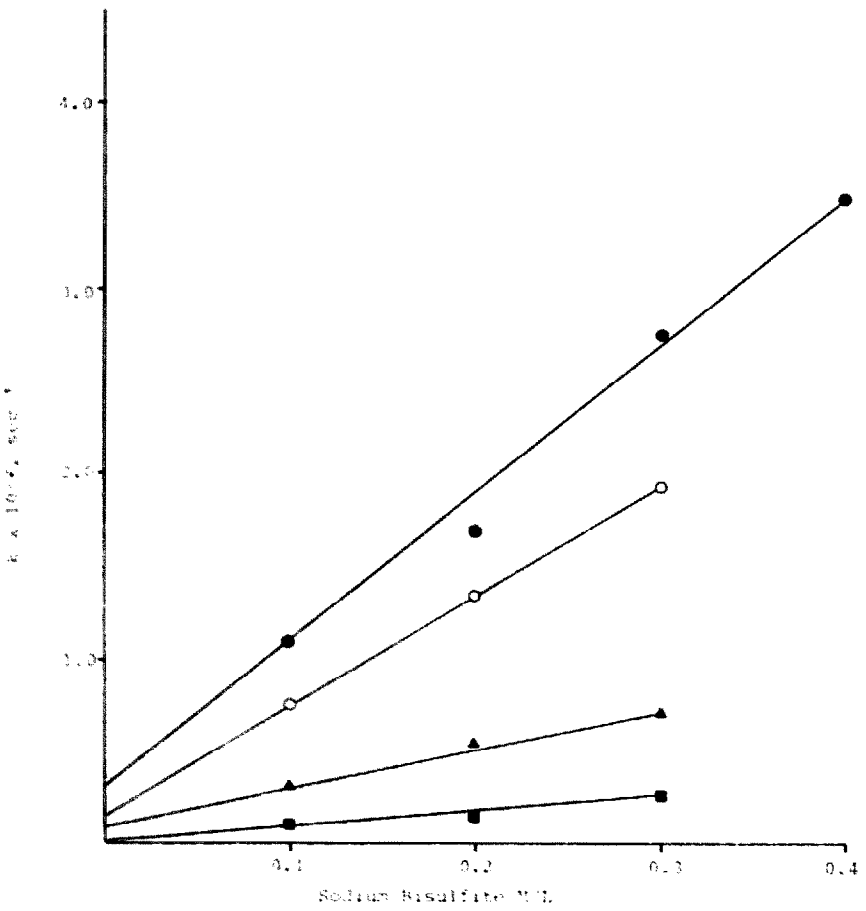


Fig. 2. The effect of bisulfite concentration on the rate of hydrolysis at 35°C of O-acetylsalicylamide at different pH values. Key: ■, pH 5.38; ▲, pH 5.77; ○, pH 6.6; and ●, pH 7.4.

sugges[illegible] in the presence of sodium bisulfite, these compounds undergo two parallel reactions and that the rate of salicylamide formation was influenced by bisulfite concentration and pH, whereas the rate of the imide formation was independent of bisulfite concentration.

Since, in the absence of bisulfite, the rate of formation of the imides was found to be first-order with respect to hydroxide in concentration and independent of buffer concentration, an integrated rate equation for the appearance of salicylamide and implicit in Scheme I can be derived for certain fixed conditions. If sodium bisulfite is in large excess over the prodrug, then at any given pH, Eqn. 6 is valid:

$$\log(A_\infty - A_t) = \log \frac{k_{obs}[\text{Bisulfite}][\text{Prodrug}]}{k_{OH}(OH)^- + k_{obs}[\text{Bisulfite}]} - \left(\frac{k_{obs}[\text{Bisulfite}] + k_{OH}[OH]^-}{2.303}\right)t \quad (6)$$

where k_{obs} is the observed second-order rate constant for the formation of salicylamide from the prodrugs and k_{OH} is the second-order rate constant for the formation of the imide. It is apparent from Eqn. 6 that a plot of $\log(A_\infty - A_t)$ (at

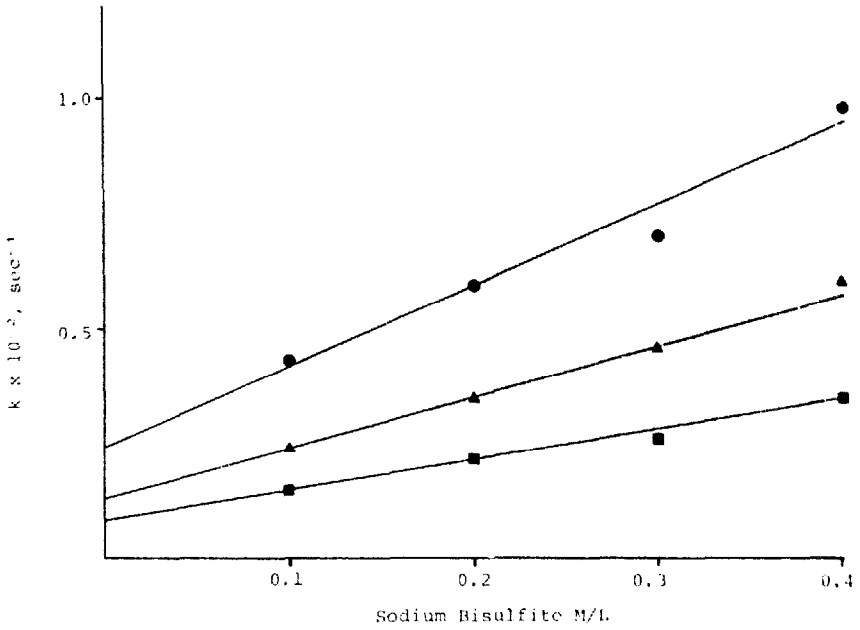


Fig. 3. The effect of bisulfite concentration on the rate of hydrolysis at 35°C of O-glutarylsalicylamide at different pH values. Key: ■, pH 6; ▲, pH 6.5; and ●, pH 6.8.

302 nm) versus time should result in a straight line. The observed overall first-order rate constant k, was calculated from the slope of the line and is equal to:

$$k = k_{obs}[\text{Bisulfite}] + k_{OH}(OH) \tag{7}$$

As expected from Eqn. 7, plots of k versus bisulfite concentrations at several pH values resulted in straight lines for both O-acetylsalicylamide and O-glutarylsalicylamide (Figs. 2 and 3, respectively). The values of $k_{OH}(OH)$ which are the observed first-order rate constants of formation of the imide were found to be in excellent agreement with the values obtained independently in the absence of bisulfite (for both O-acetylsalicylamide and O-glutarylsalicylamide).

It was apparent from the data of Figs. 2 and 3 that the slopes of such plots were dependent on the pH of the solution. If one assumes that both sulfite ion (SO_3^{2-}) and bisulfite ion (HSO_3^-) catalyze the rate of formation of salicylamide from the prodrug, then:

$$k_{obs}[\text{Bisulfite}]_T = k_{SO_3^{2-}}[SO_3^{2-}] + k_{HSO_3^-}[HSO_3^-] \tag{8}$$

Substituting for the species involved in terms of the ionization constant of bisulfite (K_a) and hydrogen in concentration:

$$k_{obs} = k_{SO_3^{2-}}\left(\frac{K_a}{(H)^+ + K_a}\right) + k_{HSO_3^-}\left(\frac{H}{(H)^+ + K_a}\right) \tag{9}$$

Using the values of k_{obs} at two pHs and calculating for the value of $k_{SO_3^{2-}}$ and $k_{HSO_3^-}$ the value of $k_{HSO_3^-}$ was found to be close to zero. This is in agreement with the findings of Munson et al. (1977) in their study of the catalytic hydrolysis of aspirin by sodium bisulfite. Therefore, Eq. 9 can be reduced to:

$$k_{obs} = k_{SO_3^{2-}} \left(\frac{k_a}{K_a + H} \right) \tag{10}$$

The second-order rate constant $k_{SO_3^{2-}}$ calculated at several pH values is shown in Table 2.

In the case of O-glutarylsalicylamide in the pH range studied, where the compound exists in its ionized form, the following equation is valid:

$$k_{obs} = k_{SO_3^{2-}} \left(\frac{K_a}{(H + K_a)} \right) \left(\frac{K'_a}{H^+ + K'_a} \right) \tag{11}$$

where K'_a (4.58×10^{-5}) is the ionization constant of the prodrug. The second-order rate constants calculated at several pH values is shown in Table 2. As it is seen from the data of Table 2, the second-order rate constant for the glutaryl sulfite reaction is slower than that calculated for the O-acetyl derivative. This is probably due to an electrostatic repulsion between the two negatively charged species. Thus, it is apparent from this study that, in the acidic and neutral pH range, bisulfite at high concentration can effectively complete with the intramolecular O → N acyl transfer.

Conclusions

In order for acyl salicylamides to be of value as prodrugs for salicylamide, the O → N acyl transfer should be slow enough so that these compounds are absorbed from the gastrointestinal tract in their intact form. The $t_{1/2}$ for the conversion of these prodrugs to the corresponding imide at pHs 4.6 and 6 was found to be approximately 64 h and 2.5 h, respectively. Consequently, it was felt that these compounds probably meet the first criteria cited in the introduction.

In the presence of human plasma or horse serum esterases, these derivatives cleave rapidly to salicylamide. Thus, it would appear that if these compounds are absorbed in their intact form, they will rapidly generate salicylamide.

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