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Kinetics of decomposition of *O*-acyl derivatives of salicylamide and related compounds

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Summary

Salicylamide hemisuccinate ethyl ester, salicylamide hemiglutarate methyl ester, *O*-acetyl-*N*-methylsalicylamide, and *O*-acetyl-*N*,*N*-diethylsalicylamide were synthesized, and the kinetics and mechanisms of their decompositions in aqueous buffers at various pH values were studied. The results support a mechanism in which the predominant feature is a transacylation reaction involving intramolecular attack of the amide anion on the carbonyl carbon of the neighboring ester group. In the case of *O*-acetyl-*N*-methyl salicylamide and *O*-acetyl-*N*,*N*-diethylsalicylamide, where the ionization of the amide group is blocked, the predominant reaction was found to be hydrolysis of the ester groups rather than *O*-to-*N*-acyl transfer. The reaction rates for the glutarate hemiester were found to be faster than those for the corresponding ethyl ester at pH values around 7.0. These results confirm a previously proposed mechanism in which a second intramolecular general acid catalysis involving the free carboxyl group on the hemiester moiety accelerates the transacylation rate.

Introduction

Babhair and Hussain (1983) have prepared three esters of salicylamide as possible prodrugs, viz. *O*-acetylsalicylamide, *O*-acetylsalicylsalicylamide and *O*-glutarylsalicylamide, and have studied their rates of decomposition both in aqueous buffers and in the presence of esterase enzymes. In buffers, the rates of formation of salicylamide from all three *O*-acylsalicylamide derivatives were negligible in the pH range 3–9, but *O*-to-*N*-acyl transfer occurred in all cases at a rapid rate. Thus, when aqueous buffer solutions were added to dioxane solutions of these compounds, a UV maximum was observed at 355 nm, and there was no UV absorbance at 302 nm where salicylamide has its maximum absorbance. The kinetics of formation of *N*-acylsalicylamides were found to be first-order with respect to the compounds and dependent upon pH, but independent of buffer concentration and ionic strength. Babhair and Hussain (1983) proposed a mechanism for the *O*-to-*N*-acyl transfer similar to that proposed for compounds containing an aromatic ureido functional group in an ortho position to an ester (Behme and Cordes, 1964; Hegarty and Bruice, 1970; Stella and Higuchi, 1973). This mechanism is represented in Scheme 1 and involves an initial rapid and reversi-

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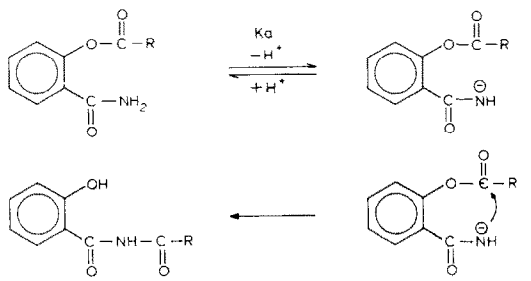


Scheme 1.

ble ionization of the amide group followed by a rate-determining nucleophilic attack of the amide anion on the ester carbonyl.

Babhair and Hussain (1983) showed that the rate of *O*-to-*N*-acyl migration was dependent upon the nature of the acyl group. For example, the rate of *O*-to-*N*-acyl transfer in the case of (2-carbamoylphenyl)-2-acetoxybenzoate was found to be slower than that observed for the corresponding acetyl derivative. This difference was rationalized on the basis of steric hindrance by the bulky *O*-acetylsalicyloyl group. The most important observation made by these authors was that even the hemiesters of salicylamide underwent *O*-to-*N*-acyl transfer rather than hydrolysis to salicylamide, despite the known fact that the carboxylate group plays an important role in the hydrolysis of hemiesters. It was suggested by these authors that the involvement of the amide group may completely mask the catalysis by the carboxylate anion.

Recently, Tawfiq et al. (1990) demonstrated the involvement of the free carboxylic acid group in the rate enhancement of *O*-to-*N* transacylation reactions of the hemiglutarate and hemisuccinate esters of salicylamide. These authors also observed that the amide anion is an extremely powerful catalyst for these base-catalyzed transacylation reactions.

The objectives of this report are to describe in detail the synthesis and pH-dependency of the hydrolysis and transacylation reactions of a series of *O*-acyl salicylamides to establish the influences of various substituent groups in the acyl and amide moieties on the rates and mechanisms of the reactions. In particular, it was thought necessary: (a) to determine the influence of free and esterified terminal carboxyl groups in the acyl moieties on the overall rates of decomposition of *O*-acyl salicylamides such as salicylamide hemisuccinate ethyl ester and salicylamide hemiglutarate methyl ester and to determine their rates of *O*-to-*N*-acyl transfer as a function of pH and in comparison with those of salicylamide hemiglutarate; and (b) to demonstrate the role of the amide anion in the *O*-to-*N* transacylation reactions of *O*-acetyl-*N*-methylsalicylamide and *O*-acetyl-*N*,*N*-diethylsalicylamide and to determine their rates and mechanisms of decomposition at various pH values in aqueous buffers.

The results of these studies are presented in this communication.

Materials and Methods

Salicylamide, ethylsuccinyl chloride, methyl-4-chloroformyl butyrate, oxalyl chloride, acetylchloride, *N*,*N*-diethylsalicylamide, glutaric anhydride, and dicyclohexylamine were purchased from Aldrich (Milwaukee, WI). Diethylether was purchased from Fisher (Fairlawn, NJ). *N*-Methylsalicylamide was purchased from K & K Labs (Plainview, NY). NMR spectra were run on a Model EM-360 or a Model 200XL instrument (Varian Instruments, Palo Alto, CA). UV spectra were run on either a Cary Model 15 or a Cary Model 118 spectrophotometer (Varian Instruments). HPLC analyses were carried out using a Model 6000A Solvent Delivery System (Waters Associates, Milford, MA), a VariChrom Detector (Varian Associates), a Rheodyne Injector (Rheodyne, Cotati, CA), and a Fisher Series 5000 Recordal recorder (Fisher, Cincinnati, OH). The column packing used for separations was Ultrasphere-octyl, 5M (Beckman Instruments, Irvine, CA).

Synthetic procedures

Synthesis of salicylamide hemisuccinate ethyl ester (1)

Salicylamide (2.75 g, 0.02 mol) was dissolved in freshly distilled pyridine (5.5 ml) with constant stirring, and the solution was cooled in a dry

ice-acetone mixture to −15 °C. A second phase consisting of ethyl succinylchloride (3.2 ml, 0.02 mol) dissolved in dry diethyl ether (5 ml) was added dropwise with constant stirring. The temperature was kept at −15 °C during the course of the addition. The reaction mixture was then stirred for 30 min at −15 °C, during which time a white oily material formed. Diethyl ether (10 ml) was added and the stirring was continued for 10 min. The resulting white gelatinous precipitate was filtered and washed several times with additional amounts of diethyl ether. The gel was suspended in 0.1 N ice-cold sulfuric acid with continuous stirring for 10 min, and the precipitate which formed was isolated by filtration, washed several times with cold distilled water, and dried in a vacuum oven. The dried material was recrystallized from an ethyl acetate : benzene mixture to give compound **1** as an amorphous powder: m.p. 83–86 °C, ^{1}H-NMR (DMSO-d_6) δ 6.95–7.80 (6H, m, aromatic H plus 2 exchangeable H atoms, reduces to 4H on addition of D_2O), 4.12 (2H, q, OCH_2), 2.72 (4H, m, $COCH_2CH_2CO$), 1.19 (3H, t, CH_3); $C_{13}H_{15}O_5N$ requires C, 58.86; H, 5.66; N, 5.28. Found, C 58.49; H, 5.72; N 5.23%.

Synthesis of salicylamide hemiglutarate methyl ester (2)

Salicylamide (2.75 g, 0.02 mol) was dissolved in freshly distilled pyridine (5.5 ml) with constant stirring, and the solution was cooled in a dry ice-acetone mixture to −15 °C. Methyl-4-chloroformyl butyrate (methylglutaryl chloride) (2.76 ml, 0.02 mol) dissolved in dry diethyl ether (5 ml) was then added dropwise, and the reaction mixture was treated in an identical manner to that described for the preparation of compound **1**. Compound **2** was obtained as a white powder, m.p. 88–91 °C, ^{1}H-NMR (DMSO-d_6) δ 7.12–7.76 (6H, aromatic H plus 2 exchangeable H atoms, reducing to 4H on addition of D_2O), 3.62 (3H, s, OCH_3), 2.60 (2H, t, $OCOCH_2$), 2.45 (2H, t, $CH_2\underline{CH_2}CO \cdot O$); 1.88 (2H, m, $CH_2\underline{CH_2}$-CH_2); $C_{13}H_{15}O_5N$ requires C, 58.86; H, 5.66; N, 5.28. Found, C 58.93; H, 5.71; N, 5.25%.

Synthesis of O-acetyl-N-methylsalicylamide (3)

N-Methylsalicylamide (1.51 g, 0.01 mol) was dissolved in methylene chloride (10 ml) and triethylamine (3 ml) was added with constant stirring. The mixture was cooled in an ice-bath, and the cold solution was treated with a solution consisting of acetyl chloride (0.785 g, 0.01 mol) in methylene chloride (3 ml), added dropwise with constant stirring (the reaction was exothermic!). Stirring was continued for 15 min and the mixture was then filtered to remove the triethylamine hydrochloride salt. The filtrate containing the desired ester was evaporated to dryness, the residue was dissolved in methylene chloride, and the solution extracted several times with 2% w/v aqueous sodium hydroxide. The methylene chloride layer was separated, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness. The resulting ester, compound **3** had m.p. 93–95 °C, ^{1}H-NMR ($CDCl_3$) δ 7.05–8.00 (4H, m, aromatic H), 6.10–6.70 (1H, b, exchangeable with D_2O, NH), 3.00 (3H, d, N-CH_3), 2.33 (3H, s, $COCH_3$); $C_{10}H_{11}O_3N$ requires C, 62.17; H, 5.69; N, 7.25. Found, C, 62.19; H, 5.79; N, 7.24%.

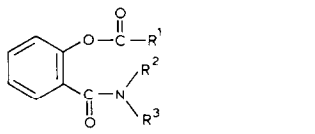
Synthesis of O-acetyl-N,N-diethylsalicylamide (4)

N,N-Diethylsalicylamide (1.93 g, 0.01 mol) was dissolved in methylene chloride (10 ml), and triethylamine (3 ml) was added with constant stirring. The mixture was then cooled in an ice-bath and acetyl chloride (0.785 g, 0.01 mol) in methylene chloride (3 ml) was added dropwise to the cold solution. The resulting mixture was treated in an identical manner to that described for preparation of compound **3**. Evaporation of the methylene chloride solution afforded compound **4** as an oil which was purified by vacuum distillation; b.p. 128 °C (0.2 mmHg). ^{1}H-NMR (DMSO-d_6) δ 7.00–7.60 (4H, m, aromatic H), 3.23 (4H, m N-$CH_2 \times 2$), 2.20 (3H, s, $COCH_3$), 1.05 (6H, q, $2 \times CH_2\underline{CH_3}$); $C_{13}H_{17}O_3N$ requires C, 66.31; H, 7.22; N, 5.95. Found, C, 66.29; H, 7.32; N, 5.87%.

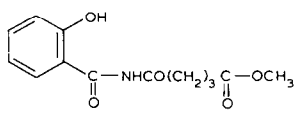
Preparation of N-(methylglutaryl)salicylamide (5) from salicylamide hemiglutarate methyl ester

Salicylamide hemiglutarate methyl ester (compound **2**) (0.5 g, 0.04 mol) was dissolved in methanol (5 ml), and phosphate buffer (0.1 M, 50 ml) at pH 8 was added. The mixture was stirred well and left at room temperature for 1 h, fol-

lowed by removal of methanol. The pH of the solution was adjusted to 3 with 0.1 N sulfuric acid with constant stirring for 10 min, during which time a precipitate formed. Stirring was continued for a further 10 min, and the precipitate was filtered, washed several times with cold water, and dried in a vacuum oven to afford compound **5**



1. $R^1 = (CH_2)_2CO{\cdot}OCH_2CH_3$, $R^2 = R^3 = H$
2. $R^1 = (CH_2)_3CO{\cdot}OCH_3$, $R^2 = R^3 = H$
3. $R^1 = CH_3$, $R^2 = H$, $R^3 = CH_3$
4. $R^1 = CH_3$, $R^2 = R^3 = CH_2CH_3$



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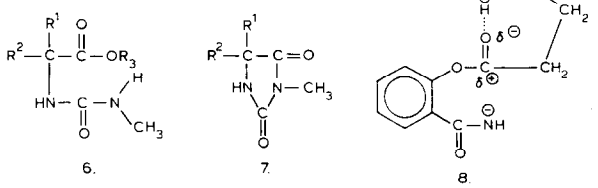


6. 7. 8.

as a white powder, m.p. 124–127 °C. ^{1}H-NMR (DMSO-d_6) δ 11.51 (1H, bs, exchangeable with D_2O, NH), 10.82 (1H, s, exchangeable with D_2O, OH), 6.92-7.95 (4H, m, aromatic H), 3.61 (3H, s, OCH_3), 2.82 (2H, m, N-CO-CH_2), 2.40 (2H, m, CH_2-COO), 1.82 (2H, m, $CH_2CH_2CH_2$). $C_{13}H_{15}O_5N$ requires C, 58.86; H, 5.66; N, 5.28. Found, C, 58.81; H, 5.50; N, 5.31%.

Kinetic studies

Rate of formation of N-acyl salicylamides from O-acyl salicylamides

In a typical run, a stock solution of *O*-acyl salicylamide was freshly prepared in spectral grade dioxane. The solution (0.1 ml) was placed in a 1 cm path-length spectrophotometer cell, and exactly 3 ml of buffer at the desired pH and ionic strength was added. The cell was then quickly inverted several times to ensure uniform mixing. When very rapid reactions were followed, the spectrophotometer cell with its content of 0.1 ml dioxane solution was placed in the cell compartment of the spectrophotometer, and while the recorder was running, 3 ml of the desired buffer was quickly injected into the cell. After addition of buffer, the increase in absorbance at 355 nm was followed as a function of time. The observed first-order rate constants were obtained by linear regression analysis of the following equation:

$$\log(A_0 - A_t)\frac{k_t}{2.303} + b$$

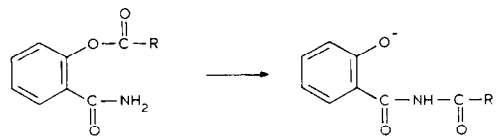
The effect of pH on the rate of formation of *N*-acyl salicylamide was determined using 0.1 M phosphate buffer. The ionic strength was adjusted to 1.0 using sodium chloride. The pH of the buffers was adjusted to the desired value by the addition of an appropriate amount of 10 N aqueous sodium hydroxide solution or 85% v/v phosphoric acid; pH values were determined using a model 611 pH meter equipped with a silver-silver chloride combination electrode; the pH of the solution was taken after the end of each run. All kinetic studies were carried out at a constant temperature (25 °C) using a circulating water bath.

Rates of hydrolysis of esters of substituted salicylamides

The rates of hydrolysis of *O*-acetyl-*N*-methylsalicylamide (**3**) and *O*-acetyl-*N*,*N*-diethylsalicylamide (**4**) were followed at the wavelengths of maximum absorbance of the corresponding phenols; i.e., 310 and 275 nm, respectively. Phosphate buffer (0.1 M) at an ionic strength of 1.0 was used to study the effect of pH on the rate of hydrolysis of these esters. The effect of buffer concentration on the rate of hydrolysis of *O*-acetyl-*N*-methylsalicylamide was studied at pH 10, 11 and 12 using phosphate buffer. The buffer concentrations were 0.1, 0.2 and 0.3 M, and the ionic strength was adjusted to 1.0 by the addition of sodium chloride.

Results

Spectrophotometric changes at 355 nm, where *N*-acyl salicylamides are known to have maximum absorbance (Babhair and Hussain, 1983), were used to measure the rate of *O*-to-*N*-acyl transfer (see Scheme 2) for the salicylamide esters. Fig. 1 shows the UV absorption spectra of the *N*-hemisuccinate ethyl ester of salicylamide in phosphate buffer at pH 7, 8, and 9 compared to those of salicylamide in the same solutions. In addition, the *N*-acyl derivative resulting from the transacylation reaction of salicylamide hemiglutarate methyl ester was isolated and characterized by m.p., elemental analysis, and NMR spectroscopy (see Materials and Methods).



Scheme 2.

The pH rate profiles for the four compounds studied are shown in Fig. 2. The ultraviolet absorption spectra of the isolated *N*-acyl derivatives were similar to those observed at the end of the reaction for solutions initially containing the *O*-acyl derivatives. The formation of the *N*-acyl products from the corresponding *O*-acyl esters (Scheme 2) was followed at their UV absorption maxima at 355 nm. The reactions were found to

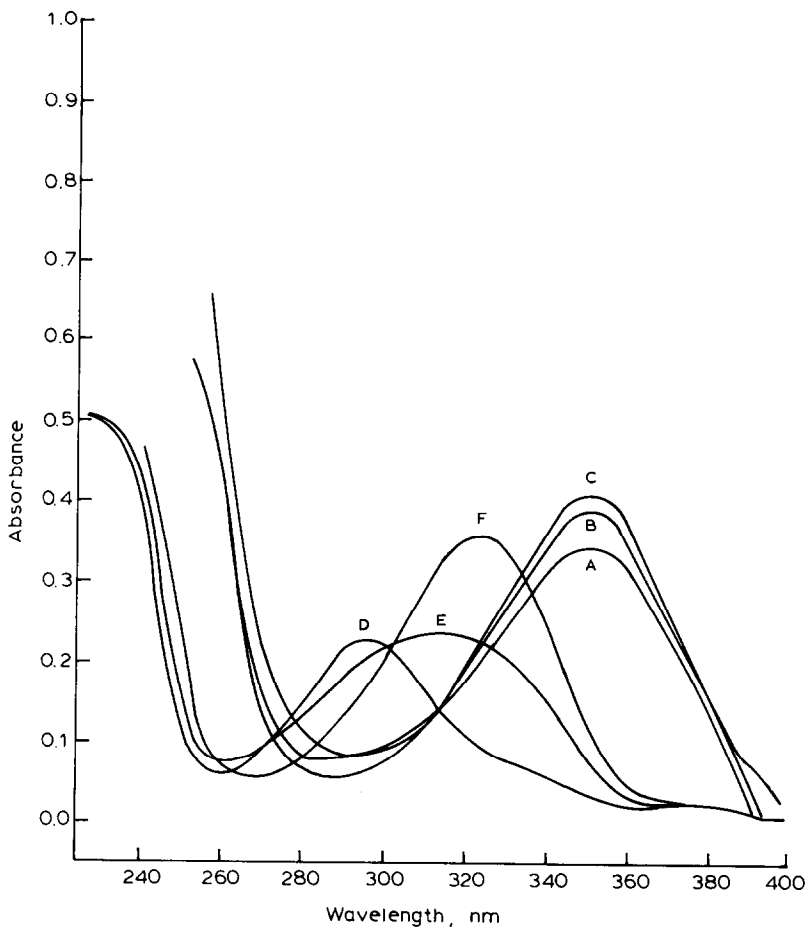
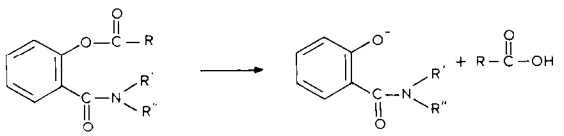


Fig. 1. UV spectra. *N*-Hemisuccinate ethyl ester of salicylamide in phosphate buffers: pH 7 (A), pH 8 (B), and pH 9 (C). Salicylamide in phosphate buffers: pH 7 (D), pH 8 (E), and pH 9 (F).



Scheme 3.

follow first-order kinetics. The effect of pH on the rate of formation of the *N*-acyl products was investigated at different pH values for the various esters. The ionic strength was adjusted to 1.0 in all the buffer solutions.

The rates of hydrolysis of *O*-acetyl-*N*-methylsalicylamide (**3**) and *O*-acetyl-*N*,*N*-diethylsalicylamide (**4**) were determined spectrophotometrically at 310 and 275 nm, respectively. This general reaction is summarized in Scheme 3, where: R = CH_3, R′ = CH_3 and R″ = H for compound **3**; and R = CH_3 and R′ and R″ = C_2H_5 for compound **4**. Fig. 3 shows the UV spectra of *O*-acetyl-*N*-methylsalicylamide in pure dioxane, in 3% (v/v) dioxane : phosphate buffer pH 9, and the spectrum of *N*-methylsalicylamide in phosphate buffer pH 9. The effect of pH on the rate of formation of phenols from compounds **3** and **4** was investigated in the pH range 8–13 (see Fig. 2). The ionic strength was adjusted to 1.0 in all buffer solutions. The effect of buffer concentration on the rate of hydrolysis of *O*-acetyl-*N*-methylsalicylamide was studied at pH 10, 11, and 12, and found to be negligible.

Discussion

The results of this study are consistent with the proposal of Babhair and Hussain (1983) who suggested that *O*-acyl salicylamides undergo *O*-to-*N*-acyl transfer at a rapid rate in aqueous solutions in the pH range 3–9. Salicylamide formation from these esters was found to be negligible in this pH range. The acyl transfer process was detected by spectral changes at 355 nm, and by HPLC and NMR spectroscopy. The formation of *N*-acyl salicylamide was found to follow first-order kinetics with respect to the esters. The pH dependency of the formation of the *N*-hemisuccinate ethyl ester of salicylamide and the *N*-hemiglutarate methyl ester of salicylamide from compounds **1** and **2**, respectively, was found to be first order

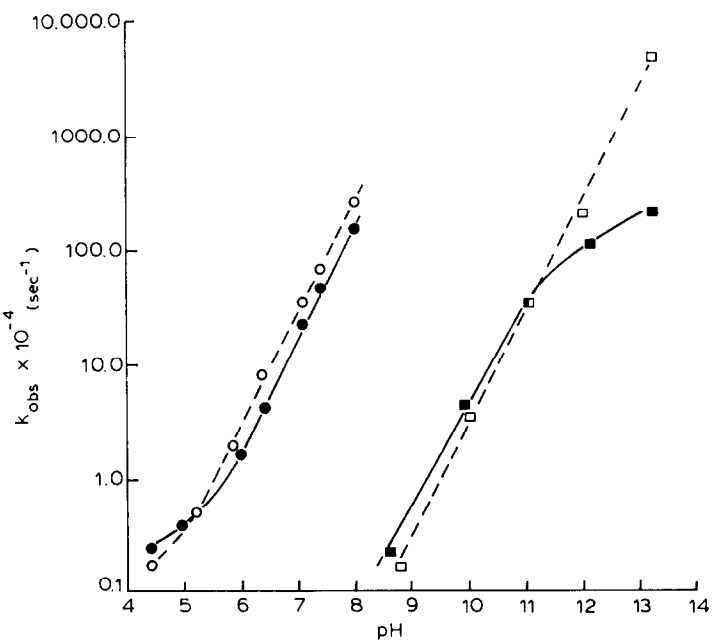


Fig. 2. pH-rate profiles in aqueous phosphate buffers. (●———●) Salicylamide hemisuccinate ethyl ester (**1**); (○- - - - -○) salicylamide hemiglutarate methyl ester (**2**); (■———■) *O*-acetyl-*N*-methylsalicylamide (**3**); (□- - - - -□) *O*-acetyl-*N*,*N*-diethylsalicylamide (**4**).

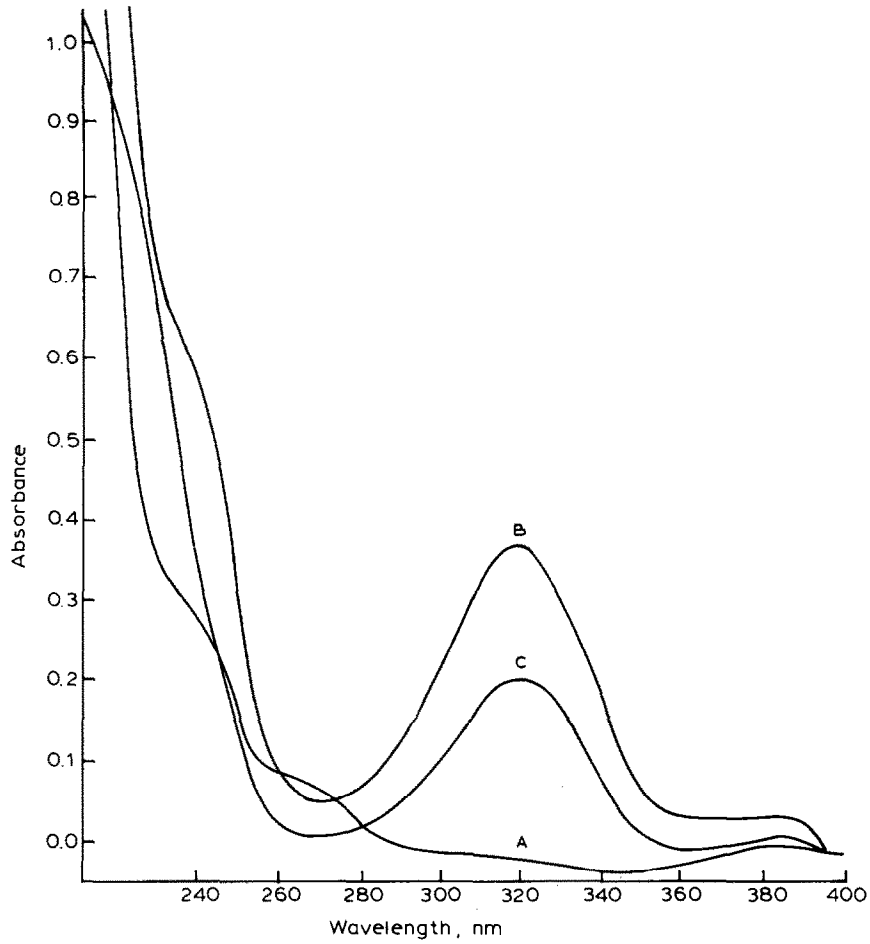


Fig. 3. UV spectra. (A) *O*-Acetyl-*N*-methylsalicylamide (**3**) in pure dioxane; (B) *O*-acetyl-*N*-methylsalicylamide (**3**) in 3% (v/v) dioxane-phosphate buffer, pH 9; (C) *N*-methylsalicylamide in phosphate buffer, pH 9.

with respect to hydroxide ion concentration in the pH range 4–15. The pH dependency deviated from linearity at pH values below pH 6, i.e., in the pH range 5.5–4, probably because of the spontaneous or water-catalyzed reaction.

The rate equation consistent with the results obtained for salicylamide hemisuccinate ethyl ester (**1**) and salicylamide hemiglutarate methyl ester (**2**) is:

$$k_{obs} = k_{H_2O} + k_{OH}\frac{K_W}{[H^+]} \qquad (1)$$

where k_{obs} is the observed first-order rate constant for the conversion of the ester to the imide, k_{H_2O} is the spontaneous or water-catalyzed rate constant, k_{OH} is the second-order rate constant for hydroxide ion catalysis, and K_W denotes the dissociation constant for water.

At high pH values, Eqn 1 will be reduced to Eqn 2:

$$k_{obs} = k_{OH}\frac{K_W}{[H^+]} \qquad (2)$$

A plot of log k_{obs} vs pH (pH rate profile) according to Eqn 2 should result in a straight line with a slope of 1. Such plots are shown in Fig. 2 for compounds 1 and 2. The pH rate profiles of these two compounds start curving in the pH

range 5.5–4.0 probably because of water catalysis. Water catalysis was also postulated by Stella and Higuchi (1973) in their study of the conversion of compounds of general structure **6** to the hydantoin, structure **7**.

The values of the second-order rate constants for hydroxyl ion catalysis for compounds **1** and **2** were calculated to be 1.57×10^4 and 2.4×10^4 l mol^{-1} s^{-1}, respectively, and the values of k_{H_2O} for compounds **1** and **2** were calculated to be 0.25×10^{-4} and 0.12×10^{-4} s^{-1}, respectively. These values are comparable to those obtained for transacylation of *O*-acetylsalicylamide and are an order of magnitude smaller than that reported for *O*-glutarylsalicylamide (Babhair and Hussain, 1983). It was postulated by Babhair and Hussain (1983) that the enhancement in the rate of the transacylation of the hemiglutarate ester is due to the involvement of the free COOH group in an intramolecular general acid catalysis, as shown in structure **8**. Upon esterification of the COOH group, as in the case of *O*-glutarylsalicylamide ethyl ester, the hydrogen bond formation illustrated in structure **8** is not possible. Consequently, as predicted, the rate of reaction of compound **2** corresponds to that found for the *O*-acetylsalicylamide.

In the case of compounds **3** and **4**, where the amide functional group is either partially or fully substituted, participation of the ionized amide in the transacylation reaction was greatly decreased. For these two compounds, hydrolysis to their corresponding phenols was the predominant reaction. Confirmation of this pathway was accomplished by HPLC analysis of the ester solutions after being exposed to buffer at pH 8.5 and 11. The results showed that disappearance of the ester peak was associated with appearance of the phenol peak without any additional peaks, suggesting that the ester was directly converted to the phenol and that no transacylation had occurred. In each case, the formation of the phenoxide ion was followed at 324 nm and showed first-order kinetics.

No buffer effect was observed in the pH range studied. However, as expected, the rates of hydrolysis of compounds **3** and **4** were found to be dependent upon pH, as shown in Fig. 2. For compound **3**, the pH rate profile begins to curve in the region above pH 11, probably because of the effect of ionization of the secondary amide functional group. The second-order rate constants due to OH catalysis, k_{OH}, were calculated for compounds 3 and 4 and were found to be approx. 3.2 l mol^{-1} s^{-1}. This value is close to the second-order k_{OH} value for the hydrolysis of phenyl acetate, which was reported to be 3.7 l mol^{-1} s^{-1} by Bruice and Mayahi (1960) and Bruice and Pandit (1960).

It is interesting to compare the reactivity of hydroxide ions toward the ester function to that of the ionized amide in an intramolecular catalysis toward the same ester group. The half-life for hydrolysis of compound **3** at pH 8.6 was 8 h, while the half-life for transacylation of *O*-acetylsalicylamide at this pH was 13 s.

The results of these studies suggest that the amide anion is an extremely powerful catalyst for base-catalyzed ester hydrolysis. In salicylamide, where the pK_a of the amide group is estimated to be greater than 11, attack of the amide anion has been shown to be the predominant mechanism in the transacylation reaction, even at pH values where a minute fraction of the anion exists. In hemiesters, where the terminal carboxyl group is sterically situated to catalyze hydrolysis of the ester group, the transacylation reaction is still favored over ester hydrolysis.

The above results may shed new light on possible mechanisms of enzyme- and protein-catalyzed ester hydrolyses. If an enzyme or protein binds an ester in such a way that an amide anion at the active site can attack the carbonyl carbon of the ester while at the same time an adjacent unionized carboxyl group at the active site can form a hydrogen bond with the carbonyl oxygen of the ester, very rapid hydrolysis of the ester may occur, and acylation of the amide may be the major product of the reaction.

The above results clearly support the previously proposed mechanism for the transacylation reaction of *O*-acyl derivatives of salicylamide, and in addition confirm (a) the involvement of the amide anion in the transacylation reaction, and (b) the catalytic role of the terminal carboxyl group in the intramolecular transacylation reaction.

Acknowledgement

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References

Babhair, S. and Hussain, A., *O*-Acylsalicylamides as possible prodrugs for salicylamide I. Kinetics and mechanisms of their degradation and reaction with enzymes and sodium bisulfite. *Int. J. Pharm.*, 13 (1983) 273–286.

Behme, M.T. and Cordes, E.H., Intramolecular participation of the amide group in ester hydrolysis. *J. Org. Chem.*, 2 (1964) 1255–1257.

Bruice, T.C. and Mayahi, M.F., The influence of the leaving tendency of the phenoxy group on the ammonolysis and hydrolysis of substituted phenyl acetates. *J. Am. Chem. Soc.*, 82 (1960) 3067–3079.

Bruice, T.C. and Pandit, U.K., The effect of geminal substitution, ring size and rotamer distribution on the intramolecular nucleophilic catalysis of the hydrolysis of monophenyl esters of dibasic acids and the solvolysis of the intermediate anhydrides. *J. Am. Chem. Soc.*, 82 (1960) 5858–5868.

Hegarty, A.F. and Bruice, T.C., Acyl transfer reactions from a ureido functional group. III. The mechanism of intramolecular nucleophilic attack of the ureido functional group upon acyl groups. *J. Am Chem. Soc.*, 92 (1970) 6575–6588.

Stella, V. and Higuchi, T., Esters of hydantoic acids as prodrugs of hydantoin. *J. Pharm. Sci.*, 62 (1973) 962–967.

Tawfiq, F.A., Dittert, L.W., Hussain, A. and Crooks, P.A., Rearrangement of *O*-acylsalicylamides via intramolecular *O* to *N* transacylation: rate enhancement by an adjacent carboxylic acid group. *J. Pharm. Sci.*, 73 (1990) 651.