generated by the addition of 5.7 g. (0.15 mole) of sodium borohydride in 150 ml. of bis-2-ethoxyethyl ether to 34.2 g. of boron trifluoride etherate (0.24 mole). Hydroborated trioleyl borate forms a glass-like, stiff gel with bis-2-ethoxyethyl ether. This unusual, clear gel is so stiff that it can easily be cut and chipped and the entrapped solvent imparts sufficient resiliency so that these chips actually bounce. They slowly fuse together on long standing and the solvent can be removed by strong heating under vacuum to give a glass-like product. Pieces of this glass also fuse together on long standing and are slowly oxidized and hydrolyzed by contact with the air.

Since this cross-linked polymer could be neither distilled nor crystallized, it could not be purified for analysis. In physical appearance, the polymers resulting from the hydroboration of both oleyl alcohol and trioleyl borate are indistinguishable.

This gel (in bis-2-ethoxyethyl ether) was heated to 160° for 20 hr., then oxidized and hydrolyzed as previously described to give 5.8 g. of C_{18}-diols, and 11.4 g. of oleyl alcohol which had not been hydroborated. Urea adduction of the diacetates showed that 13% of the diol was the 1,18-isomer.

Hydroboration, isomerization, and oxidation of I *in presence of other functional groups.* Another portion of I, 21.2 g. (0.26 mole), was hydroborated as before, but, prior to heating, oleyl alcohol, 18.7 g. (0.07 mole), was added. The solution was then refluxed for 20 hr. and oxidized to give 10.95 g. of C_{18}-diols and 21.6 g. of oleyl alcohol. Urea adduction gave a small quantity of an oil and none of the 1,18-diacetate. The same result was obtained when 2-undecanone was added prior to heating. The ketone was recovered unchanged by distillation.

In all these oleyl alcohol and trioleyl borate experiments, diol yields were quite difficult to reproduce because the polymer solidified the bis-2-ethoxyethyl ether medium, entrapping unchanged molecules and preventing further reactions with diborane. Final yields of diol therefore depend on such variables as the rate of diborane addition and the success with which the solid is broken up to permit further reaction.

Hydroboration, isomerization, and oxidation of 11-tricosene. The olefin,[12] 96.8 g. (0.3 mole), and 2.84 g. (0.075 mole) of sodium borohydride were dissolved in 200 ml. of bis-2-ethoxyethyl ether in a flask. Diborane was generated *in situ* by the slow addition of 7.55 g. (0.053 mole) of boron trifluoride etherate in 50 ml. of the same solvent. After this addition was complete, the solution was heated for 4 hr. at 185–190°. Oxidation gave the tricosanols, 65.5 g. 64% yield, m.p. 64.2–66.8° after recrystallization from ethanol.

Anal. Calcd. for $C_{23}H_{48}O$: C, 81.1; H, 14.2. Found: C, 81.2; H, 14.1.

The acetates were prepared, and repeated urea adductions showed that 80% of the product could be adducted. Saponification and recrystallization from ethanol gave *n*-tricosyl alcohol, m.p. 73.5–74.5°.[13] This product contained no secondary alcohol, as shown by infrared.

In another run, a 69-hr. heating period was employed and the yield of *n*-tricosyl alcohol, as determined by urea adduction, was 82%.

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(12) Research Division, Armour and Co., Chicago, Ill. By oxidative cleavage with periodate-permanganate, Dr. D. F. Kuemmel of our Laboratories showed that essentially all the unsaturation in this sample resides in the mid-chain position.

(13) Lit. melting point the same; P. A. Levene and F. A. Taylor, *J. Biol. Chem.*, **59**, 905 (1924).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, THE UPJOHN CO.]

The Neutral Solvolysis of the Aspirin Anion in Aqueous and Mixed Solvents

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Aspirin anion is hydrolyzed in ethanol-water to ethyl acetate, acetic acid, and salicylic acid, whereas the mixed anhydride of aspirin and acetic acid does not yield ethyl acetate under similar conditions. This further implicates ethanol in the rate determining step as previously postulated on kinetic evidence. The rate of acetic acid formation remains relatively invariant with increasing alcohol content of the media although the rate of ethyl acetate formation increases. A mechanism is proposed that rationalizes existing evidence on aspirin anion solvolysis.

There is good evidence that the mechanism of hydrolysis of the anion of acetylsalicylic acid in neutral solution, as proposed by several workers[1–3] in one form or another, is by an intramolecular attack of carboxylate ion on the carbonyl carbon of ester producing either (a) an anhydride intermediate which is subsequently rapidly hydrolyzed to salicylate and acetate or (b) a tetrahedral intermediate whose further reaction leads to products.[1,3] The former pathway has strong arguments in its favor. They have been well stated and summarized by Bender.[4] This pathway is stereochemically attractive, acetate ion is indeed a catalyst for the hydrolysis of a number of phenylacetates with a high probability of an anhydride intermediate,[5–7] and hydrolysis of aspirin anion in O^{18} labeled water should yield an expected lesser fraction of O^{18} in the final salicylate product if the intermediate anhydride cleaves as expected with nucleophile (water) attack on the acetyl carbonyl carbon of

(1) J. D. Chanley, E. M. Gindler, and H. Sobotka, *J. Am. Chem. Soc.*, **74**, 4347 (1952).

(2) D. Davidson and L. Auerbach, *J. Am. Chem. Soc.*, **75**, 5984 (1953).

(3) E. R. Garrett, *J. Am. Chem. Soc.*, **79**, 3401 (1957).

(4) M. L. Bender, *Chem. Revs.*, **60**, 53 (1960).

(5) M. L. Bender and B. W. Turnquest, *J. Am. Chem. Soc.*, **79**, 1656 (1957).

(6) T. C. Bruice and R. Lapinski, *J. Am. Chem. Soc.*, **80**, 2265 (1958).

(7) M. L. Bender and M. C. Neveu, *J. Am. Chem. Soc.*, **80**, 5388 (1958).

the mixed anhydride.[8] Also, no precedent for route (b) exists.

However, increasing the ethanol content increased the neutral hydrolysis of aspirin anion as measured by the appearance of salicylate anion and kinetic dependency on alcohol content was indicated.[3] This is difficult to reconcile with the intermediate anhydride postulate on the basis of changes in activity of the reactive intermediate by variation of the dielectric constant of the media, as increasing the dioxane concentration had little effect on the rate of salicylic acid anion appearance. The hydrolysis or alcoholysis of the presumed mixed anhydride should not be rate-determining,[4-8] and yet involvement of alcohol in the mechanism is well indicated.[3]

The mixed anhydride of salicylic acid and acetic acid could not be readily synthesized but a compound similar to the proposed hydrolysis intermediate of aspirin anion in neutral solution could be synthesized *viz.*, the mixed anhydride of aspirin and acetic acid.

This paper considers the products of hydrolysis of the mixed anhydride of aspirin and acetic acid and the products of hydrolysis of aspirin anion in alcohol-water. It also tests the proposed kinetic expression[3] for the dependence of hydrolysis rate on water and alcohol content of the hydrolytic medium.

EXPERIMENTAL

Constant pH hydrolysis of aspirin anion in varying percentages of ethanol and methanol. The Cannon di-functional titrator[9] was standardized before each run with *p*H 7.00 buffer. The acetylsalicyclic acid, *ca.* 900 mg. previously dried at 60° and high vacuum, was dissolved in the appropriate amount of methanol or ethanol. Sufficient standard sodium hydroxide was slowly added with agitation to neutralize exactly the 0.005 mole of aspirin. Subsequently, the alcoholic solution was diluted to 100-ml. volume with water previously purged with nitrogen. Fifteen milliliters of this solution was pipetted into the 25.8° thermally controlled beaker of the Cannon titrator. The *p*H control was set at 8.00 so that standard 2.00*M* sodium hydroxide did not add above this value. The microliters of 2.00*M* sodium hydroxide added were recorded as a function of time. Typical curves so obtained for varying per cent ethanol by volume are given in Fig. 1. The *p*H was maintained between 8.00 and 8.10, generally not exceeding 8.05.

Apparent first order rate constants were determined from the initial slope of the plots, S, which could be obtained in ml. of titer consumed per second. Thus

$$k(\text{sec.}^{-1}) = \frac{\text{S(Ml. NaOH)}}{\text{Ml. solution} \times \text{molarity aspirin anion}}$$

The obtained apparent first order rate constants, k, are given in Table I.

Identification of products of sodium acetylsalicylate hydrolysis in 60% ethanol (by volume) at 25°. An 0.01*M* solution of aspirin in 0.01*M* sodium hydroxide and 70% ethanol by volume was prepared and 100-ml. aliquots were extracted at

(8) M. L. Bender, F. Chloupek, and M. C. Neveau, *J. Am. Chem. Soc.*, **80**, 5384 (1958).

(9) J. B. Neilands and M. D. Cannon, *Anal. Chem.*, **27**, 29 (1955).

TABLE I

APPARENT FIRST ORDER RATE CONSTANTS FOR THE FORMATION OF ACETIC ACID FROM ASPIRIN ANION[a] AT *p*H 8.0 AND 25.8°

% Ethanol in Ethanol-water	10^6k (sec.$^{-1}$)	% Methanol in Methanol-water	10^6k (sec.$^{-1}$)
0	3.69[b]	0	3.98[c]
10	3.88	10	3.96
20	3.47	20	3.73
30	3.51	30	3.33
40	3.61	40	3.14
50	3.33		
60	3.04		
70	2.66		

[a] Although the rate constants for acetic acid formation from aspirin anion hydrolysis are reasonably invariant with increasing ethanol concentrations, actual yields of acetic acid are expected to lessen. If $k(\text{sec.}^{-1}) = k_0 + k_{ROH}[ROH]/[H_2O] = 3.65 \times 10^{-6} + 2.55 \times 10^{-6}[C_2H_5OH]/[H_2O]$ at 25°,[3] then at the completion of solvolysis the mole yield of ethyl acetate per mole of aspirin anion at varying per cent ethanol by volume should be respectively: 0.00, 0%; 0.27, 20%; 0.60, 40%; 0.75, 60%; 0.88, 80%. Obviously, the yield of titrateable acetic acid from aspirin anion hydrolysis will fall off from the initial zero order rate with time, the more so the higher the ethanol content of the solvent (see Fig. 1). Also, the first order rate constants of this Table I which are estimated from the initial slopes or apparent zero order rates will be given lower apparent values the higher the ethanol content of the solvent. [b] At *p*H 6.9 at 25° from ref. 3. [c] At *p*H 8.6 at 25° from ref. 3.

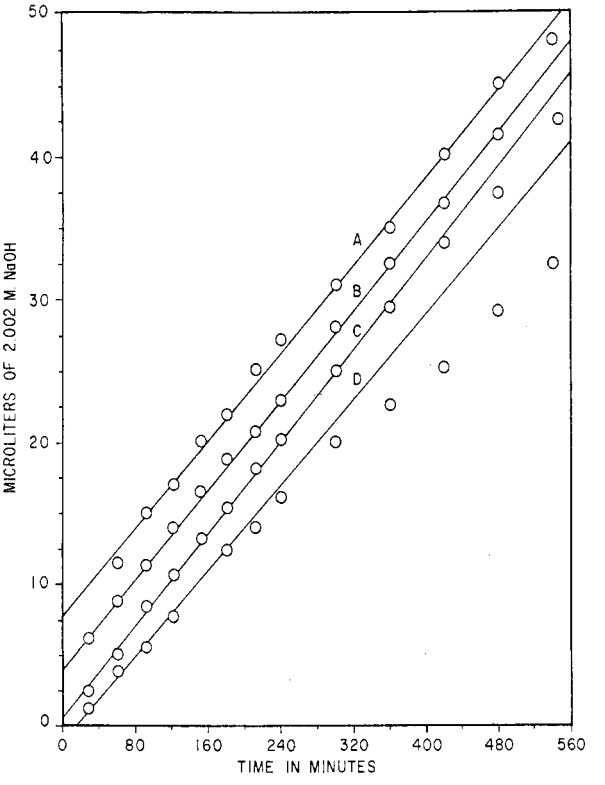


Fig. 1. The consumption of microliters of 2.002*M* sodium hydroxide by 15 ml. of 0.05*M* aspirin anion at an apparent *p*H of 8.00 at 25.8° as a function of time. The curves and the per cent ethanol (by volume) in the ethanol-water solvent are: A, 10%; B, 20%; C, 40%; and D, 60%

intervals with: (a) three separate 25-ml. benzene fractions; these fractions were collected over anhydrous calcium chloride. (b) three separate 25-ml. chloroform fractions; these fractions were collected over anhydrous calcium chloride.

A similar control study was performed in 0.5% ethanol by volume. At 0, 4, 8, 24, and 48 hr. the solutions were run in the infrared and the amounts of ethyl acetate appearing calculated as based on standard solutions of ethyl acetate in the organic solvents. The chloroform solutions gave confusing results due to the probable interaction of the drying agent—calcium chloride, with the alcohol contaminants. The dried benzene extracts, however, clearly showed the presence of ethyl acetate and the amounts are given as per cent of possible total stoichiometric transformation of acetylsalicylate to ethyl acetate in 60% ethanol in Table II.

TABLE II

COMPARISON OF FORMATION OF ETHYL ACETATE AND EXPECTED SALICYLIC ACID PRODUCTION ON THE HYDROLYSIS OF ASPIRIN ANION IN 60% ETHANOL–40% WATER AT 25°

Time in Hours	% of Possible Complete Formation of Ethyl Acetate[a]	% Hydrolysis of Aspirin Anion fom U. V. Appearance of Salicylic Acid[3]
0	0	0
4	19	18
6	35	33
24	91	70
48	90	92

[a] Corrected for blank value of an apparent 8% as ethyl acetate at zero time and given as the percentage of the total possible yield of ethyl acetate when the reaction is completed on the assumption of a stoichiometric yield of ethyl acetate and salicylate anion from aspirin anion. The 24 and 48-hr. values as obtained indicate that the estimates err on the high side since the total hydrolysis to salicylate and acetate anions and ethyl acetate as estimated by the rate constant $k = 14.3 \times 10^{-6}$ sec.$^{-1}$ at 25°[3] should be less at 24 hr. Obviously, the per cent of possible formation of ethyl acetate cannot exceed the per cent of total hydrolysis at any given time. Experimental reasons for this mild inconsistency are given in the text.

The lag in preparation for infrared analysis should tend to make these values higher than actual. However, these data for ethyl acetate formation compare very well with the data for per cent hydrolysis of aspirin as previously determined from previous ultraviolet spectrophotometric studies where the apparent first order rate constant was determined as 14.3×10^{-6} sec.$^{-1}$ in 60% ethanol at 25° at an apparent *p*H of 9.4 where the acetylsalicyclic acid exists as the sodium salt.[3]

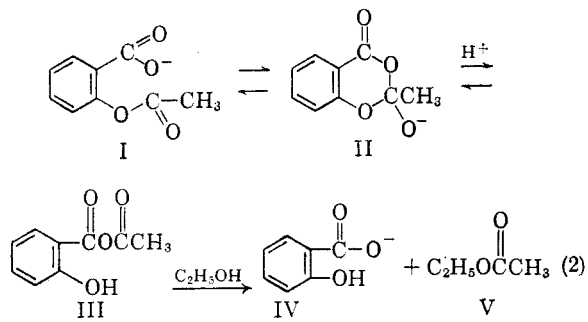
The 0.5% ethanolic solution of the sodium acetylsalicylate showed no evidence of ethyl acetate or of an anhydride when treated and investigated similarly.

An additional study by vapor phase chromatography was conducted on a 40% ethanolic solution made up with 6.98 *p*H aqueous phosphate buffer so that the final concentration was 1 g. of aspirin/100 ml. with an apparent *p*H of 8.27. After the solution stood for 48 hr., a chromatogram of this sample corresponded to a chromatogram of a prepared mixture of 40% ethanol, 60% water, and 0.4% ethyl acetate (*ca.* 0.046*M*). As the original aspirin solution was 0.055*M*, this is further proof of the almost stoichiometric formation of ethyl acetate by the hydrolysis of sodium acetylsalicylate in high concentrations of ethanol.

Attempted identification of ethyl acetate on the hydrolysis of the mixed anhydride of aspirin and acetic acid. A 60% ethanolic solution with water of the mixed anhydride of aspirin and acetic acid was prepared and permitted to stand for 24 hr. until hydrolysis had been assured. There was no indication of any ethyl acetate on analysis by vapor phase chromatography.

DISCUSSION

Considerations relative to the mechanism of the neutral hydrolysis of the aspirin anion. In general, nucleophilic attack on an ester carbonyl carbon is inhibited by solvents of decreasing dielectric constant.[10] The anomalous increase in rate of salicylate ion appearance on the aqueous neutral hydrolysis of aspirin anion with increasing ethanol content[3] is contrary to expectation. The fact that no such increase occurs with increasing dioxane content[3] implies direct involvement of ethanol in the solvolytic mechanism. The experimental evidence of this paper further implicates ethanol in the mechanism, as the rate of production of ethyl acetate parallels the rate of production of salicylate ion (see Table II). The ethyl acetate formation could be attributed to the preferential alcoholysis over hydrolysis of the presumed mixed anhydride intermediate[1-3] where ethanol is not involved in the rate determining step of the hydrolysis, *i.e.*



However, a similar mixed anhydride, that of acetylsalicylic and acetic acids, gave no indication of any ethyl acetate as a product of hydrolysis in 60% ethanol-water (by volume). If it is assumed that the mixed anhydride of acetic and salicylic acids would act similarly, the above mechanism in (2) does not appear probable.

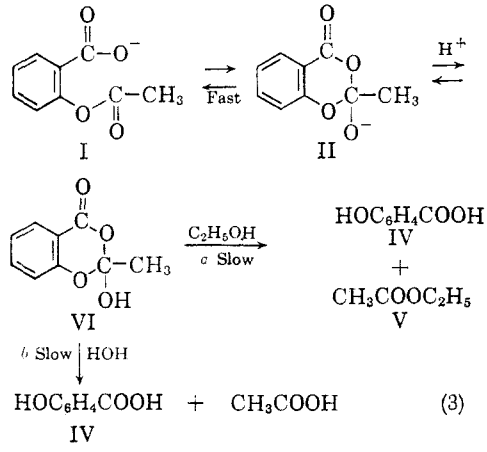
Even if this negative evidence is ignored, it would not be expected that at 60% ethanol by volume (0.3 mole fraction of ethanol) more than 50% of the aspirin anion, I, would be alcoholyzed[11] to ethyl acetate, V, through the mixed anhydride, III. Yet, the aspirin anion was largely transformed to ethyl acetate (see Table II).

The major items that must be considered are that ethanol is kinetically and structurally involved in the soloolysis of aspirin anion and enhances the rate.

(10) *Tables of Chemical Kinetics: Homogeneous Reactions*, National Bureau of Standards Circular 510, U. S. Department of Commerce, Washington, D. C., 1951 and Supplement 1, 1956.

(11) J. Koskikallio, *Acta Chem. Scand.*, **13**, 665 (1959).

A possible mechanism that could account for the kinetic evidence has been proposed[3] but no precedent exists for the postulated further reaction of the hydrated cyclic intermediate with ethanol in a rate determining step. A more probable mechanism consistent with the kinetic dependencies[3] could be:



(3)

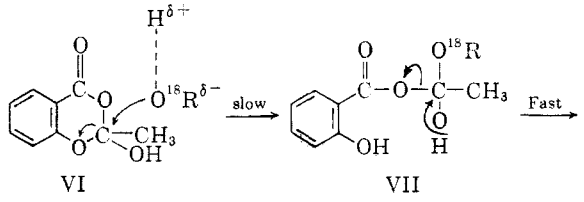
The step II to VI has been predicted by Davidson and Auerbach.[2]

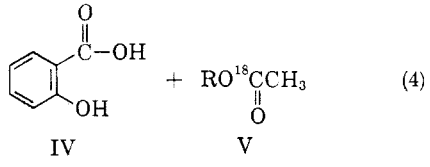
In this mechanism, the rate determining step *a*, the S_N2 reaction of ethanol with VI to form salicylic acid and ethyl acetate, would be faster than the rate determining step *b*, the S_N2 reaction of water with VI to form salicylic acid and acetic acid. Thus the over-all rate would increase with increasing ethanol concentration.

It is necessary to rationalize Bender's evidence[8] that aspirin anion hydrolyzed in H_2O^{18} produces salicylic acid containing a minimum of the O^{18}. This isotopic evidence can be rationalized with the kinetic dependency on water and ethanol[3] and with an ethyl acetate product [see (4) and (5)]. Both routes are kinetically equivalent where the rate-determining step is the attack of the nucleophile on the uncharged cyclic intermediate, VI. Ethanol, R = C_2H_5, would have to be a better attacking group than water, R = H, increasing the over-all rate of aspirin anion solvolysis in increasing ethanol concentrations.

Some possible simultaneous attack of H_2O^{18} on the phenyl carbonyl could occur and yield aspirin anion, I from II which would again equilibrate and enter the sequence II → VI → IV + V. This could readily account for the small amount of O^{18} appearing in the salicylic acid product.[8]

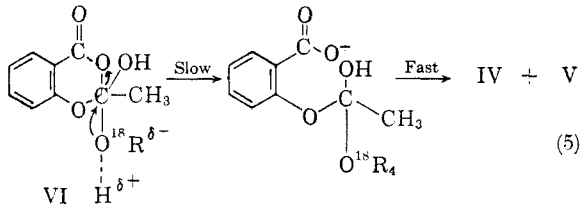
The rate of standard alkali consumption at constant *p*H shows that the apparent first order rate of appearance of a neutralizable acidic group,





(4)

or by:



(5)

presumably acetic acid, from the hydrolysis of aspirin anion is relatively constant with varying ethanol and methanol concentrations in alcohol-water. However, the over-all rate of salicylic acid appearance is not.[3] These facts are consistent with the over-all reaction rate constant[3]

$$k = k_0 + k_{ROH}[ROH]/[H_2O] \quad (6)$$

where [ROH] is the molarity of alcohol in the alcohol-water solvent. The first term on the right, k_0, accounts for the constant first order rate of acetic acid appearance in varying alcohol-water solvents while the second term expresses an apparent dependence of the rate of ethyl acetate formation on a function of the alcohol concentration.

It can be argued that the near constancy of the aspirin anion solvolysis by water in water-alcohol and in water-dioxane[3] is due to the near balancing of two opposing factors—*viz.*, the effective concentration or activity of the reactive cyclic intermediate, VI— is increased to about the same degree that the concentration of the nucleophile water is decreased, where

$$k_0 = k'[VI][HOH] \quad (7)$$

Acknowledgment. The author is greatly indebted to Mrs. Lillian G. Snyder, Mr. Marvin F. Grostic, and Mr. George E. Bronson for excellent technical assistance, and acknowledges with pleasure discussion with Dr. M. L. Bender.

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