on pumice was assembled as described earlier and heated to 320°. At this temperature, a feed comprising 2.11 mmol of ethylene/min and 7.18 mmol of nitrogen/min was passed through the reactor for 3 min. This reduced part of the cupric chloride so that both Cu(I) and Cu(II) chlorides were present. The system was purged with nitrogen for 30 min. A micro gas scrubbing bottle, containing 120 μl of the appropriate dichloride was connected between the nitrogen line and the reactor. Nitrogen was then passed through the scrubbing bottle at 9.29 mmol/min. The nitrogen, now containing dichloride vapor, passed through the reactor with the same contact time as the olefins described previously. The product was trapped in a Dry Ice–acetone bath and analyzed by gas chromatography or infrared spectroscopy in the usual way.

Rate of 1,2-Dichloroethane Formation from Ethylene and Cupric Chloride.—Ethylene was chlorinated by cupric chloride impregnated on pumice according to the procedures described earlier. Helium was introduced at the end of the reaction zone at 9.29 mmol/min. This diluted the product stream such that 1,2-dichloroethane remained in the vapor phase. The product was collected in gas-sampling bottles over one 2-min and two 3-min time intervals. The product was then analyzed by gas chromatography using calibrated response factors relative to nitrogen. Nitrogen is used as the internal standard because it is metered into the reactor at a known rate which does not change during the reaction. Therefore, the rate of product formation, the rate of ethylene consumption, and the material balance can be determine from the integrated band areas.

Rate of Chlorine Production from Cupric Chloride on Pumice.—The pumice to be used in this experiment was heated in air at 550° for 20 hr to oxidize any organic matter which might be present. It was then impregnated with cupric chloride in the usual way. It was then heated to 320 in the reactor described earlier in a stream of nitrogen (9.89 mmol/min). The effluent was directed into two gas scrubbers containing aqueous potassium iodide solution. This was done for three successive 2-hr runs. After each run, the liberated iodine was titrated with standard sodium thiosulfate solution. The rate of chlorine evolution was nearly constant (0.018 ± 0.001 mequiv/2 hr).

Registry No.—Cupric chloride, 7447-39-4; *trans*-ethylene-d_2, 1517-53-9; *cis*-2-butene, 590-18-1; *trans*-2-butene, 624-64-6; **1**, 16622-55-2; **2**, 16622-56-3.

Acknowledgment.—Our thanks to Dr. P. Zakriski for performing the mass spectrometric analyses, to Dr. J. Burr for his help with the infrared spectra, and to Professor P. Bartlett for his helpful discussions.

Synthesis and Hydrolysis Kinetics of Lincomycin Acetals

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A series of *para*-substituted O-benzylidene acetals at the 3,4 position of the antibiotic lincomycin was synthesized in search of an easily cleaved acetal. The hydrolysis reactions of these acetals follow pseudo-first-order kinetics and appear to follow the generally accepted mechanism for simple acetal hydrolysis. The pH-rate profile for the acetal containing a *p*-phenolic substituent indicates that the hydronium ion catalysis of the phenolate ion form as well as the phenol form of the derivative has to be considered. The second-order rate constants of hydrolysis for the series of arylidene derivatives at 70° gave a correlation coefficient of 0.996 in a modified Hammett σ^+ plot with a ρ value of −1.85. From this correlation a σ^+ value of −3 is estimated for the *p*-phenolic oxy anion. The use of arylidene derivatives as protective groups is discussed.

Benzylidene acetals of polyfunctional molecules are commonly used as protective groups.[1] In search of an easily cleaved acetal of lincomycin, the effect of substituents on the rate of hydrolysis of arylidene acetals was studied since Kreevoy and Taft[2] only quantitated the substituent effect for numerous aliphatic acetals and ketals. While the study was being completed, an article by Fife and Jao[3] was published in which the effect of substituents on the rates of hydrolysis of cyclic and acyclic arylidene acetals were found to give plots of log *k* *vs.* σ or σ^+ with curvature for *para*-substituted compounds. In the present study with *para*-substituted 3,4-O-benzylidene acetals of lincomycin, a correlation coefficient of 0.996 was obtained in a modified Hammett σ^+ plot. This type of correlation is useful in the selection of acetals to use as protective groups.

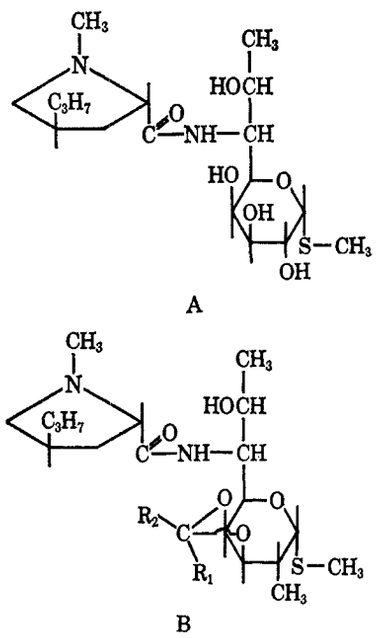
The antibiotic lincomycin proved to be an ideal molecule in which to study the effect of substituents on the rates of acetal hydrolysis, since acetals are easily formed with the *cis* hydroxyls on C_3 and C_4 of lincomycin (see Figure 1). In addition, the analytical problem was simplified by the lack of an intense uv chromophore in lincomycin. A range of hydrolysis rates is provided by the following substituents in the *para* position of 3,4-O-benzylidenelincomycin: chloro, hydrogen, methyl, methoxy, and hydroxyl.

(1) J. F. W. McOmie, *Advan. Org. Chem.*, 191 (1963).
(2) M. M. Kreevoy and R. W. Taft, Jr., *J. Amer. Chem. Soc.*, **77**, 5590 (1955).
(3) T. H. Fife and L. K. Jao, *J. Org. Chem.*, **30**, 1492 (1965).

Results

Synthesis and Structure Determination of the Lincomycin Acetals.—Acetals are commonly prepared by catalysis with strong acids, dehydrating agents ($ZnCl_2$, etc.), and in some cases with neutral amine salts of strong acids (NH_4Cl, etc.). Since lincomycin is somewhat unstable in strong acid media, acetal formation was attempted using lincomycin–HCl with excess aldehyde without any additional acid. Acetal formation was found to occur readily under these conditions in virtually quantitative yield when benzene was used to remove the water azeotropically.

The lincomycin acetals were initially isolated as the hydrochloride salts, but only the *p*-chloro-, -hydrogen-, and -methyl-substituted 3,4-O-benzylidene derivatives could be recrystallized as the hydrochloride salts. The less stable acetals, such as the 3,4-O-(*p*-hydroxybenzylidene) and the 3,4-O-anisylidene derivatives, decomposed rapidly on attempted recrystallization from hydroxylic solvents, yielding lincomycin–HCl. Recrystallization of the hydrochloride salts from nonhydroxylic solvents was difficult since the lincomycin acetals are very insoluble in most of these solvents. Consequently, the 3,4-O-anisylidene and 3,4-O-(*p*-



A

B

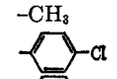
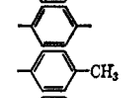
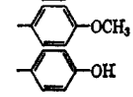
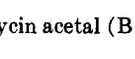
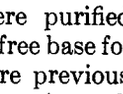
	R_1	R_2
I, 3,4-O-isopropylidenelincomycin	$-CH_3$	$-CH_3$
II, 3,4-O-(*p*-chlorobenzylidene)-lincomycin		-H
III, 3,4-O-benzylidenelincomycin		-H
IV, 3,4-O-*p*-toluylidenelincomycin		-H
V, 3,4-O-anisylidenelinocmycin		-H
VI, 3,4-O-(*p*-hydroxybenzylidene)-lincomycin		-H

Figure 1.—Lincomycin (A) and lincomycin acetal (B) structures.

hydroxybenzylidene) acetals were purified by crystallization after conversion to the free base form.

Nmr and chemical studies were previously used to establish the structure of lincomycin and 3,4-O-isopropylidenelincomycin (see Figure 1).[4] The lincomycin bis(N-ethylcarbamate) prepared from anisylidenelincomycin and ethyl isocyanate was identical with the lincomycin 2,7-bis(N-ethylcarbamate)[5] prepared from 3,4-O-isopropylidenelincomycin and ethyl isocyanate as shown by identical ir spectra, melting points, and tlc R_f values. The location of the anisylidene moiety is thus at the 3,4 position of lincomycin (see Figure 1).

The asymmetric benzylic carbon introduces the possibility of forming two diastereoisomeric acetal derivatives. The quasi-equatorial phenyl isomer (relative to the sugar ring), as shown in Figure 1, is considered to be the preferred structure of the derivative, and this is in accord with predictions of greater thermodynamic stability for equatorial phenyl-1,3-dioxan derivatives of cyclic sugars.[6] Dreiding models of the quasi-axial phenyl isomer show a 1,3-diaxial interaction and a generally greater steric hindrance than does the quasi-equatorial phenyl isomer.

Four out of the five *para*-substituted O-benzylidene derivatives (II, III, IV, and V) reported herein have

(4) H. Hoeksema, B. Bannister, R. D. Birkenmeyer, F. Kagan, B. J. Magerlein, F. A. MacKellar, W. Schroeder, G. Slomp, and R. R. Herr, *J. Amer. Chem. Soc.*, **86**, 4223 (1964).

(5) D. G. Martin, U. S. Patent 3,271,385 (Sept 6, 1966).

(6) A. B. Foster, A. H. Haines, J. Homer, J. Lehmann, and L. F. Thomas, *J. Chem. Soc.*, 5005 (1961).

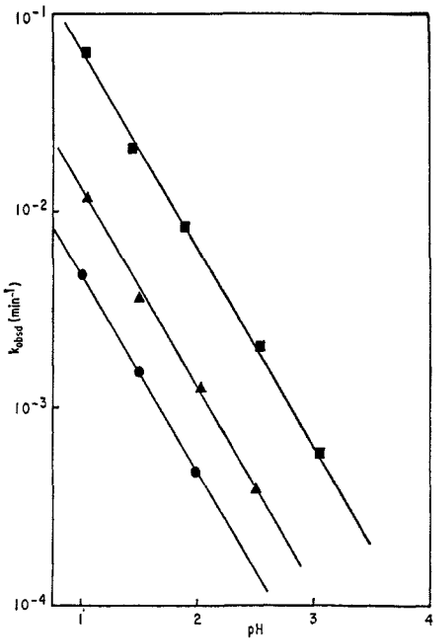


Figure 2.—Plots of log k (min^{-1}) *vs.* pH at 37° and μ = 0.1 for ■, 3,4-O-*p*-toluylidenelincomycin; ●, 3,4-O-(*p*-chlorobenzylidene)lincomycin; ▲, 3,4-O-benzylidenelincomycin.

only one signal in the nmr spectrum at 367 cps for the benzylic proton. Since the acetal moiety of V is at the 3,4 position of lincomycin and has a single benzylic proton signal at 367 cps, II, III, and IV are also at the 3,4 position of lincomycin and have the same stereochemistry about the benzylic carbon. The last compound, *p*-hydroxybenzylidenelincomycin acetal, has a benzylic proton signal at 367 cps and at 352 cps besides additional division of other peaks, which indicates a two-component mixture. One component appears to be the same type of isomer as II, III, IV, and V. The second component could be a diastereoisomer, a positional isomer, or a degradation product.

Differential kinetic analysis[7] of the mixed isomers of *p*-hydroxybenzylidenelincomycin showed the ratio of fast to slow hydrolyzing isomers to be 3:2. Using this ratio 3:2 and the areas under the nmr benzylic proton signals, the slow and fast hydrolyzing isomers can be assigned to the signals at 367 and 352 cps, respectively. Since the 3,4-lincomycin acetals II, III, IV, and V have a benzylic proton signal at 367 cps, it is implied that the slowly hydrolyzing isomer is 3,4-O-(*p*-hydroxybenzylidene)lincomycin. This is also in agreement with the kinetic data (to be shown later) where the second-order rate constant for the slowly hydrolyzing isomer fits the modified Hammett σ^+ correlation, whereas the fast hydrolyzing isomer does not.

Hydrolysis Kinetics of Lincomycin Acetals.—The second-order rate constants for hydrolysis at 37° are given in Table I and the pH-rate profiles in Figures 2 and 3. The pseudo-first-order plots for the acetals II–V were linear for 95% of the reaction. For VI (*p*-hydroxybenzylidenelincomycins) the initial portion of the kinetic plot is curved, but the plot for the last 25% of the reaction is linear. This type of kinetic plot is resolved by the method of residuals[7] (see Figure 4).

(7) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1961, pp 162–164.

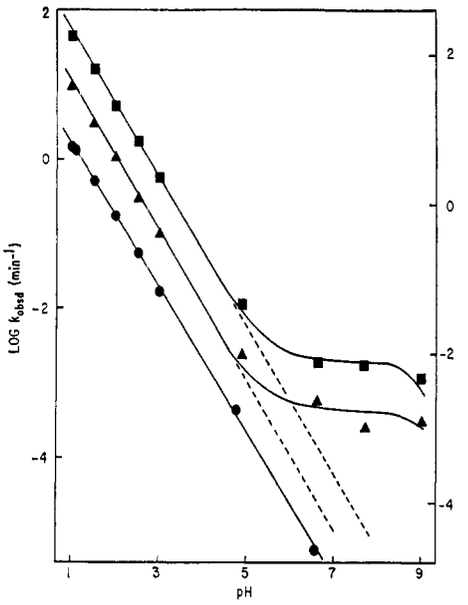


Figure 3.—Plots of log k (min^{-1}) *vs.* pH at 70° and μ = 0.1 for ●, 3,4-O-anisylidenelincomycin (right-hand ordinate scale); ▲, 3,4-O-(*p*-hydroxybenzylidene)lincomycin (left-hand ordinate scale; ■, fast hydrolyzing isomer of *p*-hydroxybenzylidenelincomycin (left-hand ordinate scale).

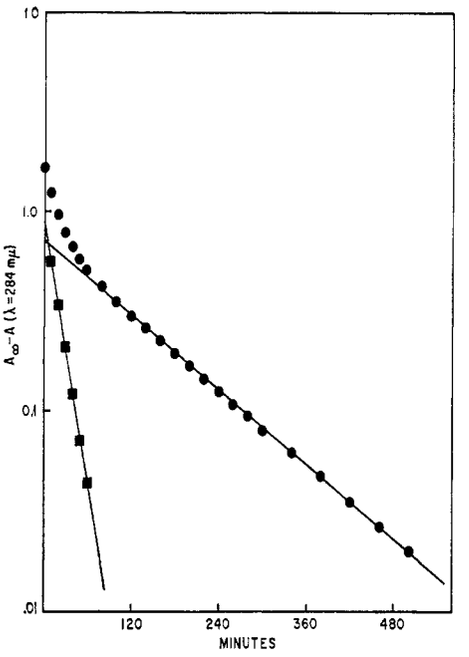


Figure 4.—First-order plot for the hydrolysis of *p*-hydroxybenzylidenelincomycin acetal at 37°, pH = 3.03, and μ = 0.1. The curve is resolved into a two-component system by the method of residuals.

TABLE I

HYDROLYSIS RATE CONSTANTS AT 37° AND μ = 0.1

Compound	Slope of pH-rate profile	Second-order rate constant, sec^{-1} M^{-1}
3,4-O-(*p*-Chlorobenzylidene)lincomycin (II)	−1.04	0.00093
3,4-O-Benzylidenelincomycin (III)	−1.03	0.0024
3,4-O-*p*-Toluylidenelincomycin (IV)	−1.02	0.0120
3,4-O-Anisylidenelincomycin (V)	−0.98	0.0732
p-Hydroxybenzylidenelincomycin (VI)		
3,4-O-Acetal	−1.00	0.127
Fast acetal (isomer of VI)	−0.98	0.813

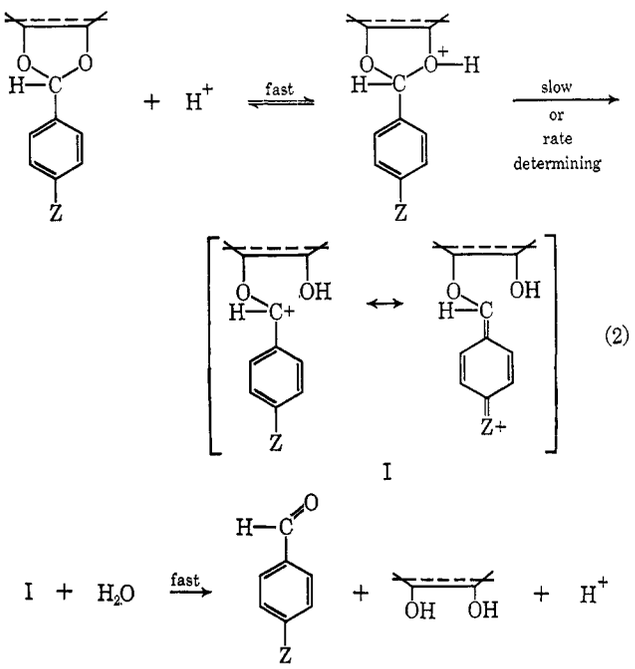
Because of the decreased rate of reaction, the rate constants for 3,4-O-(*p*-hydroxybenzylidene)lincomycin and 3,4-O-anisylidenelincomycin were determined at 70° instead of 37° in the pH range 7–9. To obtain a log k *vs.* pH plot over the whole pH range 1–9, the 37° rate constants were extrapolated to 70° by using linear graphs of ln k vs. $1/T$ for 37, 42, 47, and 55°.

Discussion

Mechanism of Lincomycin Acetal Hydrolysis.—The pH profiles for all the acetals are straight lines with slopes approximately equal to −1 in the pH range 1.0–3.5 at 37° and μ = 0.1 (Figures 2 and 3). In Figure 3 the pH profile is linear over the pH range 1–7 for 3,4-O-anisylidenelincomycin, but for the *p*-hydroxybenzylidenelincomycins the pH profiles deviate from linearity at pH 6, indicating a change in reaction mechanism. The data in the pH range 1–3.5 for the hydrolysis of all the acetals are in agreement with the rate law

$$\text{rate} = \frac{d[\text{acetal}]}{dt} = k[H^+][\text{acetal}] \qquad (1)$$

The generally accepted mechanism for hydrolysis of alkylidene derivatives[8,9] is a rapid, reversible protonation of an acetal oxygen followed by a rate-determining heterolysis to a carbonium ion and an alcohol molecule with rapid decomposition of the carbonium ion to products. A similar mechanism, eq 2, can be written for arylidene acetals. The important difference is that the charge on the carbonium ion is stabilized by resonance with the aryl groups in addition to charge stabilization by the alkoxy group.



(2)

Both the preequilibrium and the rate-determining step in the acetal hydrolysis mechanism 2 should be greatly aided by electron-releasing groups in the alde-

(8) M. M. Kreevoy and R. W. Taft, Jr., *J. Amer. Chem. Soc.*, **77**, 3146 (1953).

(9) F. Stasiuk, N. A. Sheppard, and A. N. Bourns, *Can. J. Chem.*, **34**, 123 (1956).

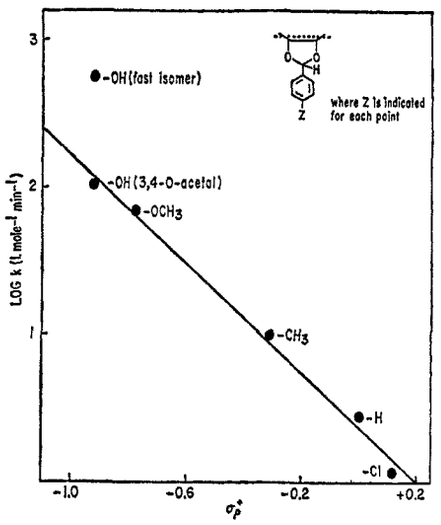
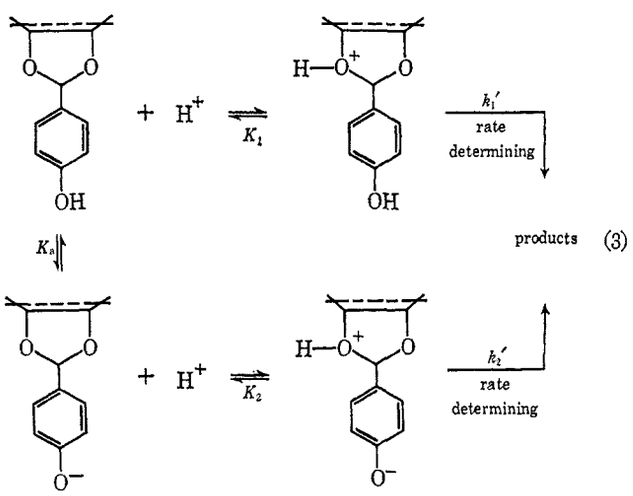


Figure 5.—Semilogarithmic plot of pH-independent rate constants at 70° *vs.* σ_p^+ values for the hydrolysis of lincomycin acetals.

hyde portion of the acetal, which serve to increase the basicity of the acetal and stabilize the carbonium ion intermediate. Since the hydrolysis of the phenolate anion form of *p*-hydroxybenzylidenelincomycin acetal should be extremely rapid, it offers a simple explanation for the deviation from linearity in the pH-rate profiles. Mechanism 3 illustrates the reactions under consider-



ation. If [A] = concentration of acetal, [AH] = concentration of acetal in undissociated form, [A$^-$] = [A] − [AH] = concentration of acetal as phenolate anion, K_a, K_1, and K_2 are defined as dissociation constants, and $k_1 = k_1'/K_1$ and $k_2 = k_2'/K_2$, then k_{obsd} is given by eq 4. Since the reversible protonations K_1 or

$$k_{obsd} = \frac{k_1[H^+]}{1 + \frac{K_a}{[H^+]}} + \frac{k_2[H^+]}{1 + \frac{[H^+]}{K_a}} \quad (4)$$

K_2 and the rate-determining heterolysis steps k_1 or k_2 are not presently separable, only rate constants k_1 or k_2, which are functions of both steps, can be determined. Equation 4 fully describes the pH-rate profile for *p*-hydroxybenzylidenelincomycin shown in Figure 3. A similar mechanism was used by Bender and Silver[10] to explain the pH-rate profile for the hydrolysis of 2-*p*-hydroxyphenyl-1,3-dioxanes.

(10) M. L. Bender and M. S. Silver, *J. Amer. Chem. Soc.*, **85**, 3006 (1963).

The phenolic ionization constant (K_a) for 3,4-O-*p*-hydroxybenzylidenelincomycin was determined at 70°. in a thermostated Cary cell from spectrophotometric data.[11] The values of k_1 and k_2 for *p*-hydroxybenzylidenelincomycin were calculated using eq 4 and the apparent K_a. They are listed in Table II. In Figure 3 the points for the *p*-hydroxybenzylidenelincomycin acetals are experimental, and the solid line is the calculated curve for eq 4 using the parameters in Table II. In the case of the 3,4-O-anisylidene derivative, the pH-rate profile continues to exhibit linearity as the pH is increased and can be completely described by rate eq 1 as expected for the *p*-methoxy group.

TABLE II

KINETIC CONSTANTS ($sec^{-1}\ M^{-1}$) FOR *p*-HYDROXYBENZYLIDENELINCOMYCINS AT 70° AND μ = 0.1

pK_a = 9.11, 9.01, 8.99; average = 9.04

k_1 (3,4-O-acetal) = 1.72 $sec^{-1}\ M^{-1}$

k_1 (fast acetal) = 9.17 $sec^{-1}\ M^{-1}$

Calculated k_2 using eq 5	pH 6.61	pH 7.69	pH 9.00	Average
k_2 (3,4-O-acetal)	1.01 × 10^4	4.6 × 10^3	1.11 × 10^4	8.6 × 10^3
k_2 (fast acetal)	3.17 × 10^4	3.22 × 10^4	4.90 × 10^4	3.8 × 10^4

Modified Hammett σ^+ Correlation.—As mentioned previously, acetal hydrolysis mechanisms 2 and 3 should be greatly aided by electron-releasing groups in the aryl portion of the acetal. To quantitate the effect of electron-donating substituents and support mechanisms 2 and 3, plots of log k *vs* σ^+ values were constructed according to the modified Hammett equation, eq 5. The σ^+ values were taken from ref 12

$$\log k - \log k_0 = \rho\sigma^+ \quad (5)$$

and are given in Table III, along with the second-order rate constants at 70°.

TABLE III

ACTIVATION PARAMETERS, σ_p^+ VALUES AND pH-INDEPENDENT RATE CONSTANTS FOR LINCOMYCIN ACETAL HYDROLYSIS

Compd no.	Phenyl substituent	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$,[a] eu	σ_p^+	k, sec^{-1} M^{-1} at 70°
II	*p*-Cl	19.3	−14.0	+0.114	0.0192
III	*p*-H	18.9	−13.6	0	0.046
IV	*p*-CH_3	16.6	−17.3	−0.311	0.164
V	*p*-OCH_3	17.6	−11.0	−0.778	1.14
VI	*p*-OH (fast acetal)	15.5	−12.9	−0.92	9.17
	p-OH (3,4-O-acetal)	16.4	−12.8	−0.92	1.72
	p-O$^-$ (fast acetal)				3.8 × 10^4
	p-O$^-$ (3,4-O-acetal)				8.6 × 10^3

[a] Calculated at 37° with rate constant units of $sec^{-1}\ M^{-1}$.

The pH-independent rate constant for the hydrolysis of the *p*-phenolate anion acetal was estimated at 70°, but its temperature dependence was not determined. Therefore, the pH-independent rate constants for the other *para*-substituent acetals were extrapolated to 70° and used in the modified Hammett σ^+ correlation in Figure 5. The Hammett plot at 70° has the constants ρ = −1.85 and log k_0 = 0.367. With these parameters and the rate constant at 70°, a σ_p^+ value of −3.0 can be estimated for the phenolic oxyanion, which reflects its very large electron-donating ability.

The pH-independent rate constants at 70° have correlation coefficients of 0.962 and 0.996 for σ and σ^+

(11) D. H. Rosenblatt, *J. Phys. Chem.*, **58**, 40 (1954).

(12) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 90.

values, respectively. At 37° the correlation coefficients are 0.971 and 0.994 for σ and σ^+, respectively. The higher correlation coefficient for σ^+ indicates a direct resonance interaction between the substituent and the reaction center and that the transition state has carbonium ion character.

The activation parameters are listed in Table III and were calculated by applying eq 6. The adherence of the data to eq 6 is shown in Figure 6. The activation enthalpies are within the range obtained for other acetals.[3] The activation entropies are negative values for the hydrolysis of lincomycin acetals, but comparing the structural effects on the entropy of activation in Table IV one would expect $\Delta S^{\pm}$ to be negative and utilize the A-1 reaction.[3,13]

$$k = \frac{\kappa kT}{h} e^{\Delta S^{\pm}/R} e^{-\Delta H^{\pm}/RT} \qquad (6)$$

TABLE IV
ACTIVATION ENTROPIES FOR HYDROLYSIS OF VARIOUS ACETALS

Compound	$\Delta S^{\ddagger}$,[a] eu
Dimethyl acetal	+13.1[b]
Dimethyl formal	+6.8[b]
Diethyl formal	+6.9[b]
Benzaldehyde diethyl acetal	+1.0[c]
2,2-Dimethyl-1,3-dioxolane	+7.9[d]
2-Methyl-1,3-dioxolane	+5.6[d]
1,3-Dioxolane	−0.6[d]
2,4,4,5,5-Pentamethyl-1,3-dioxolane	−3.8[d]
2-Phenyl-1,3-dioxolane	−8.9[c]
3,4-O-Benzylidenelincomycin	−13.6

[a] Entropies calculated at 25, 30, or 37°. [b] J. Koshikallio and E. Whalley, *Trans. Faraday Soc*, **55**, 809 (1959). [c] See ref 3. [d] P. Salomaa and A. Kankaanperä, *Acta Chem. Scand.* **15**, 871 (1961).

Aryl Acetals as Protective Groups.—Unsubstituted benzylidene acetals are occasionally unsuitable as protective groups owing to acid-catalyzed migration of esters under the conditions required to remove the acetal.[14] The $t_{1/2}$ of the 3,4-O-(*p*-hydroxybenzylidene)lincomycin acetal (VI) is approximately 50 times less than the unsubstituted benzylidene acetal III (Table V). Other workers have shown that certain substituted benzylidene acetals hydrolyze faster than the corresponding unsubstituted benzylidene acetal.[15,16] The present observation, that σ^+ values are directly related to the rates of hydrolysis of the acetals, may facilitate the choice of the proper substituted benzylidene acetal and extend their utility as protective groups.

TABLE V
HALF-LIVES ($t_{1/2}$) OF *para*-SUBSTITUTED 3,4-BENZYLIDENELINCOMYCIN ACETALS AT pH 1.0 AND 37°

Compd no.	$t_{1/2}$, min	σ^+
II	124	+0.114
III	48.1	0.0
IV	9.64	−0.311
V	1.58	−0.778
VI	0.91	−0.92

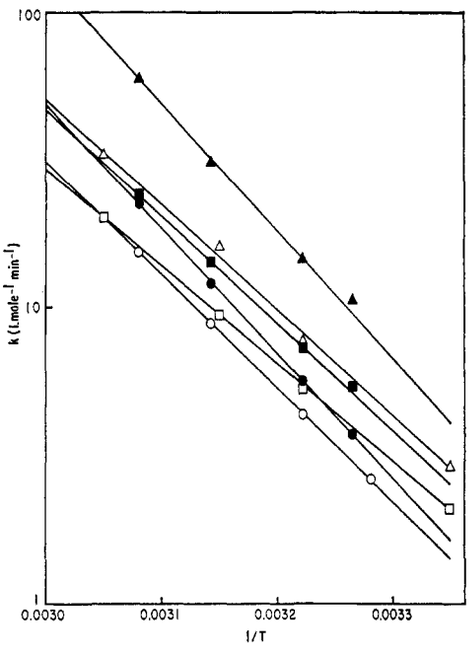


Figure 6.—Arrhenius plots of the second-order pH-independent rate constants for the acidic hydrolysis of ▲, 3,4-O-benzylidenelincomycin (0.01); ●, 3,4-O-(*p*-chlorobenzylidene)lincomycin (0.01); ■, 3,4-O-*p*-toluylidenelincomyin (0.1); ○, 3,4-O-anisylidenelincomycin (1.0); △, 3,4-O-(*p*-hydroxybenzylidene)lincomycin (1.0); □, fast hydrolyzing isomer of *p*-hydroxybenzylidenelincomycin (10.0) (multiply ordinate scale by the numbers in parentheses).

Experimental Section

Table VI records the analytical properties of the lincomycin acetals. The acetals were synthesized by essentially the same procedure as described below in the synthesis of V. Acetals II, III, and IV were isolated as the hydrochloride salts and recrystallized from methyl cellosolve by rapidly cooling a saturated solution of the acetal prepared from hot Methyl Cellosolve. The acetal IV was converted into the free base and chromatographed on a column of Florisil followed by elution with methyl ethyl ketone. The solvent was removed and the compound recrystallized as described below.

For the pK_a determination and the kinetic studies at the alkaline pH's, the two components of *p*-hydroxybenzylidenelincomycin acetal were partially separated by chromatography on a column of carboxymethylcellulose resin with a linear gradient of triethylamine acetate (pH 8) from 0.05 to 0.10 *M*.

3,4-*O*-Anisylidenelincomycin Base (V).—A solution of 47.0 g of lincomycin hydrochloride hemihydrate dissolved in mixture of 125 ml of dimethylformamide, 75 ml of anisaldehyde, and 160 ml of benzene was heated in a bath at 140°. The benzene–water azeotrope was allowed to distil at 105–110° and, upon collecting each 50 ml of distillate, an additional 50 ml of dry benzene was added. Crystallization slowly occurred after 100 ml of distillate was collected and, after an additional 250 ml of distillate was collected, the reaction flask was allowed to cool to room temperature. The pale brown reaction mixture was treated with 200 ml of ether, and the solids were isolated by filtration and washed with ether. The yield of crude white 3,4-O-anisylidenelincomycin–HCl, after drying at 40° under vacuum, was 43.0 g (82% of theory). Tlc (silica gel, acetone–ether 8:2) showed one major spot with trace contaminants of lincomycin and anisaldehyde.

A suspension of 21.0 g of 3,4-O-anisylidenelincomycin–HCl in 150 ml of water was shaken with 15 ml of 2 *N* sodium hydroxide in a separatory funnel. The product was extracted with four 400-ml portions of ether. The ether extracts were combined, dried well with sodium sulfate, and concentrated to 100 ml by

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Table VI

Properties of the *para*-Substituted Benzylidene Derivatives of Lincomycin

Compd no.	Substituent	Formula	Equiv wt Calcd	Equiv wt Found	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % S	Calcd, % Cl	Found, % C	Found, % H	Found, % N	Found, % S	Found, % Cl
II	*p*-Cl[a]	$C_{25}H_{38}N_2O_6SCl_2$	567.6	567	53.09	6.77	4.95	5.67	12.54	52.24	7.10	4.65	5.63	11.79
III	*p*-H[a]	$C_{25}H_{39}N_2O_6SCl$	531.1	532	56.53	7.40				55.66	7.59			
IV	*p*-CH_3[a]	$C_{26}H_{41}N_2O_6SCl$	545.1	541	57.28	7.58	5.56	5.88	6.50	56.03	7.76	5.58	5.95	6.31
V	*p*-OCH_3	$C_{26}H_{40}N_2O_7S$	524.6	524	59.53	7.69	5.34	6.10		59.77	7.66	5.34	6.17	
VI	*p*-OH	$C_{25}H_{38}N_2O_7S$	510.7	498	58.80	7.50	5.49	6.28		58.11	7.76	5.42	6.16	

[a] Hydrochloride salts.

distillation. Crystallization was induced with seed crystals. After standing in the refrigerator overnight, the white needlelike crystals were removed by filtration and washed with ether–hexane 1:1. The recovery was 13.2 g after drying at 65° under high vacuum. An additional 4.7 g of product was obtained by adding hexane to the mother liquor giving a total recovery of 17.9 g. Tlc on silica gel G (acetone–ether, 8:2) showed a single compound with R_f 0.8. The compound was recrystallized by dilution of an acetone–ether solution of the compound with hexane.

Kinetic Measurements.—The hydrolysis of lincomycin acetals was followed by observing the appearance of aldehyde in the ultraviolet region of the Cary Model 11 or 15 spectrophotometers. Table VII shows that the progress of the hydrolysis reactions can be followed by observing the appearance of the product spectrophotometrically, since the molar absorptivity of reactant is small compared to that of the product.

In the acidic pH region the rates were fast enough to allow following the complete reaction on the Cary recording spectrophotometer. The Cary 5-cm cell was thermostated to the required temperature within ±0.5°. In the pH region 7–9 the reaction solutions were sealed in ampoules and thermostated in a 70° oil bath for the required times and then assayed on the Cary. The A_∞ values for the 70° runs were calculated from the initial concentration of acetal. The buffers used were chloride for pH 1–3, acetate for pH 3–7, and phosphate for pH 7–9. Potassium chloride was used to adjust the ionic strength to 0.1.

Table VII

Molar Absorptivities of Lincomycin Acetals and Corresponding Aldehydes at the Wavelength of Maximum Absorbance of the Aldehyde

Product	Product, λ_{max}, mμ	a_M (product)	a_M[a] (reactant)
Benzaldehyde	249	11,200	186
p-Chlorobenzaldehyde	260	16,100	247
p-Methoxybenzaldehyde	285	16,800	236
p-Tolualdehyde	262	16,100	275
p-Hydroxybenzaldehyde	284 (pH 1–5)	15,800	500 (pH 1–5)
p-Hydroxybenzaldehyde	330 (pH 9–10)	27,000	400 (pH 9–10)

[a] Molar absorptivity of the lincomycin acetal at λ_{max} of the corresponding aldehyde.

Registry No.—II HCl, 16315-42-7; III HCl, 16315-43-8; IV HCl, 16394-31-3; V, 16315-44-9; VI, 16315-45-0.

Some Structural and Acidity Relationships in Olefinic Carboxylic Acids

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In an attempt to resolve some contradictions between reported experimental data and arguments which relate acidity and structure in β-substituted acrylic acids, the *cis–trans* isomer pairs of β-methyl-, β-ethyl-, β-isopropyl-, β-*t*-butyl-, and β-phenylacrylic acids, and *cis*- and *trans*-2-methylcyclopropanecarboxylic acids were prepared and their dissociation constants were determined by potentiometric titration. The results are shown in Table II. In contrast with earlier reports, the *cis*- and *trans*-β-methylacrylic acids (crotonic acids) have essentially the same dissociation constants. The results remove an inconsistency as to the effect of a *cis*-β-methyl group on the acidity of α,β-olefinic acids, and it is suggested that replacement of a *cis*-β hydrogen by a methyl group results in a decrease in acidity of 0.43–0.44 pK. The general trend in difference of acidity between *cis* and *trans* isomers with increasing size of β substituent is consistent with steric interaction between the *cis*-β substituent and the carboxyl group resulting in an increasing twisting of the carboxyl group out of the olefinic plane.

Attempts to correlate structural features and acidity in carboxylic acids and then interpret the correlations have fascinated chemists over the years. One such correlation, that *cis* isomers of α,β-olefinic carboxylic acids are more acidic than the corresponding *trans* isomers, has been explained by Ingold[2] in terms of steric inhibition of resonance. Thus, "On account of size only we expect a methyl, or a phenyl, or a chlorine substituent, if *cis*-related to the carboxyl group, to cause a twisting of the latter out of the ethylenic plane, and thus to strengthen the acid."[2] That is, the noncoplanarity of the ethylenic and carboxyl groups interferes with the conjugation between these groups which results in destabilization of the acid relative to the corresponding anion, and consequently an increase of acidity. Some doubts about the completeness of this explanation have been raised.[3] Specifically, using published values of acidity constants,[4] it is difficult to see why replacement of a *cis*-β hydrogen by a methyl group should result in ΔpK values of +0.15, +0.43, −0.37, and +0.43 in acrylic acid, *trans*-crotonic acid, methacrylic acid, and *trans*-β-ethylacrylic acid. That is, steric inhibition of resonance, a *cis*-β-methyl group interacting with a carboxyl group, seems to be inadequate to explain acidity changes of different size and even different sign brought about by a constant change in structure. The present work was carried out in order to examine systematically acidity relationships in *cis–trans* pairs of α,β-olefinic carboxylic acids and to use the

(1) Based on the M.S. Thesis of E. A. McCoy.

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(4) Taken from the values compiled in Table II by McCoy and Nachtigall.[3]