CH_3(18)), 1.16 (s, CH_3(17)), 2.01 (s, CH_3CO-), 4.74 (dd, J = 10.4, 6.9 Hz, H(3)). Recrystallization from ethanol-hexane at -20 °C gave colorless prisms, mp 95.5-97 °C.

Attempted Acid Hydrolysis of 7. To 2 mg of epoxy acetate **7** was added 0.5 mL of tetrahydrofuran (distilled under N_2 from Na) and 0.2 mL of 7% perchloric acid. The mixture was heated in a Microflex vial for 4 days at 55 °C, at which time TLC indicated the absence of starting **7** and appearance of a more polar product. Product isolation with ether (aqueous NaCl wash, $MgSO_4$) and chromatography on Florisil with 10% ethyl acetate in hexane afforded 1.5 mg of a solid which showed no ester absorption in the IR: mass spectrum (70 eV) m/z (relative intensity) 304 (M^+, 12), 271 (22), 260 (24), 205 (32), 189 (70), 81 (100); ^1H NMR δ 3.56 (dd, J = 10.2, 7.0 Hz, H(3)). These data suggest the retention of the epoxide and the acid-catalyzed hydrolysis of the acetate to the epoxy alcohol 8.

3-Keto-15-rippertene (9). To a stirred, 5-10 °C solution of 9.5 mg of alcohol **5** in 0.4 mL of spectrograde acetone was added dropwise Jones' reagent until TLC indicated absence of starting material. Excess Jones' reagent was quenched with 1 drop of 2-propanol, the solvent was removed, and the crude oil was chromatographed on Florisil with 5% ethyl acetate-hexane to give 9 mg of ketone **9** which was homogeneous by TLC and GLC. ^1H NMR showed the absence of the H(3) carbinyl proton and methyl resonances at δ 0.94 (d, J = 7 Hz), 0.99 (d, J = 7 Hz), and 1.27 (s, s, CH_3 (17), (18)). Mass spectrum (70 eV): m/z (relative intensity) 286 (M^+, 61), 271 ($M^+ - CH_3$, 100). Measurement of the CD spectrum of a 1:10 dilution of the 9 mg of ketone in 5 mL of purified hexane gave $\Delta\epsilon_{310} = +2.87$, $\Delta\epsilon_{301} = +3.51$, and $\Delta\epsilon_{293} = +3.37$. Multiple Cotton effects for β,γ-unsaturated ketones have also been observed for testosterone derivatives.[10]

X-ray Structure Determination of 7. The data crystal of 3α-acetoxy-15-epoxyrippertane, a colorless prism obtained from hexane-ethanol at -20 °C, was mounted on an Enraf-Nonius CAD 4A diffractometer under the control of a PDP 11/45 computer system and subjected to Cu X radiation (λ = 1.5418 Å). The space group was $P2_12_12_1$ with a = 11.202 (1) Å, b = 28.575 (7) Å, c = 6.299 (2) Å, and Z = 4 and ρ_{calcd} = 1.14 g/cm^3. The data were reduced (p = 0.04), and the structure was solved by using the MULTAN direct-method series, using the programs of the Enraf-Nonius structure determination package developed chiefly by Okaya and Frenz. Of the 1899 reflections measured ($0° < 2\theta < 72°$), 1167 with $F_o^2 > 3\sigma(F_o^2)$ were used in the subsequent refinement, which converged to values of 0.047 and 0.051 for R and R_w respectively. Fractional atomic coordinates are presented in Table II. The thermal parameters, bond angles and distances, and observed and calculated structure factors can be obtained as supplementary material.

Acknowledgment is made to the National Science Foundation (Grant DEB-7823257) and to the University Awards Committe/Joint Awards Council of the State University of New York for financial support of this work. We also thank Drs. T. Eisner and R. Silberglied for *N. ephratae* soldiers, Mr. D. Lawler for 360 MHz NMR spectra, and Dr. C. Iden and Mr. P. Chang for mass spectra.

Supplementary Material Available: Atomic parameters (Table SI), important bond distances and bond angles (Table SII), and observed and calculated structure factors (Table SIII) (10 pages). Ordering information is given on any current masthead page.

Structure-Reactivity Studies on the Equilibrium Reaction between Phenolate Ions and 2-Aryloxazolin-5-ones: Data Consistent with a Concerted Acyl-Group-Transfer Mechanism

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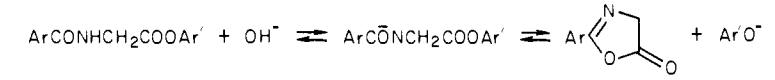
Abstract: The rate and equilibrium constants for the reaction between phenolate anions and 2-aryloxazolin-5-ones have been measured as a function of the structures Ar and Ar′. The change in "effective" charge on both phenol-leaving oxygen and



endocyclic oxygen from ground to transition state, as determined from the relevant Brønsted parameters, is substantial and essentially additive consistent with a concerted displacement mechanism. The stepwise mechanism requires a small change in effective charge on the phenol oxygen because departure of phenolate ion from the tetrahedral intermediate cannot be rate limiting. Hydroxide ion attack on the C-5 atom of the oxazolinone to yield a benzoylglycine has a Hammett σ^- dependence which can only arise from a concerted displacement; the rate-limiting step for the stepwise mechanism is the addition of hydroxide and the transition state of the rate-limiting step will therefore not involve much endocyclic C–O bond fission. An inverse deuterium oxide solvent isotope effect indicates that the observed general-acid catalysis has a specific-acid/nucleophilic mechanism; both hydroxide and oxonium ion catalysis are demonstrated by using ^{18}O-labeling experiments to involve nucleophilic attack at the carbonyl (C-5) center. The equilibrium constant for reaction of azide ion with 2-phenyloxazolin-5-one has been measured; it is suggested that the absence of racemization during azide coupling in peptide synthesis is related to the very unfavorable equilibrium constant for oxazolinone formation compared with that of activated oxygen esters.

Introduction

The ring closure of acyl-α-amino acids to yield unsaturated oxazolin-5-ones was first investigated by Plöchl[1a] and Erlenmeyer[1b] and later by Mohr and Geis[1c] for the saturated species. Work in the past decade[1d,2,3] has indicated that activated esters of acyl-α-amino acids hydrolyze in alkali through the oxazolinone. Williams and Young[4] have shown that aryl acyl-α-amino acid esters undergo a readily reversible reaction to yield oxazolinone and phenol in basic solutions in chloroform. In recent years the

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Table I. Physical and Analytical Properties of Substrates[g]

substituent[f]	mp/°C[h]	found/% C	found/% H	found/% N	formula	requires/% C	requires/% H	requires/% N
			4-Nitrophenyl-Substituted Hippurates					
3-nitro	138-139	52.3	3.3	12.1	$C_{15}H_{11}O_7N_3$	52.2	3.2	12.2
3-chloro	153-154	53.8	3.3	8.4	$C_{15}H_{11}O_5ClN_2$	53.8	3.3	8.4
4-methyl	148-149	60.8	4.5	8.8	$C_{16}H_{14}O_5N_2$	61.1	4.5	8.9
parent	167-168[a]	59.8	3.8	9.2	$C_{15}H_{12}O_5N_2$	60.0	4.0	9.3
4-chloro	183-184	53.7	3.4	8.2	$C_{15}H_{11}O_5ClN_2$	53.8	3.3	8.4
4-methoxy	178-179	58.1	3.9	7.8	$C_{16}H_{14}O_6N_2$	58.4	4.5	8.2
4-nitro	178-179	52.4	3.0	12.2	$C_{15}H_{11}O_7N_3$	52.2	3.2	12.2
			2-Substituted Phenyloxazolin-5-ones					
parent	87-89[b]							
4-chloro	130-132[c]							
4-methyl	101-101.5[d]							
4-methoxy	124-127	63.3	4.7	7.3	$C_{10}H_9NO_3$	62.8	4.7	7.3
3-chloro	91-92	55.2	2.9	7.1	$C_9H_6ClNO_2$	55.3	3.1	7.2
4-nitro	151-152[e]	52.3	2.9	13.4	$C_9H_6N_2O_4$	52.4	2.9	13.6
3-nitro	153-154	52.2	2.5	13.5	$C_9H_6N_2O_4$	52.4	2.9	13.6

[a] From a previous study. [b] From benzene, lit. mp 86 °C. M. Crawford and W. T. Little, *J. Chem. Soc.*, 729 (1959). [c] From ligroin, lit. mp 121-122 °C (reference in footnote *b*). [d] From benzene/ligroin, lit. mp 101-101.5 °C (reference in footnote *b*). [e] From benzene, lit. mp 112-114 °C. M. M. Botvinnik and S. M. Avaeva, *Org. Khim.*, 288 (1950) (*Chem. Abstr.* **49**, 3943*i* (1955)). [f] Hippuric acids used as intermediates in these syntheses are 4-nitro (ethanol, mp 131-132 °C. N. J. Novello, S. R. Miriam, and C. P. Sherwin, *J. Biol. Chem.*, 67, 555 (1926)), parent (mp 187 °C from B. D. H. Ltd., Poole), 4-chloro (water, mp 145-146 °C, lit. mp 143 °C, reference as for 4-nitro), 3-chloro (water, mp 145-147 °C, lit. mp 143-144 °C, reference as for 4-nitro), 4-methoxy (water, mp 170-171 °C, lit. mp 170 °C, A. J. Quick, *J. Biol. Chem.*, 97, 403 (1932)), 3-nitro (water, mp 165-166 °C, lit. mp 165-167 °C, J. B. Muenzen, L. R. Cerecedo, and C. P. Sherwin, *J. Biol. Chem.*, 67, 473 (1926), and 4-methyl (water, mp 161 °C, lit. mp 161-162 °C, R. Pfleger and G. Markert, *Chem. Ber.*, 90, 1482 (1957)). [g] Analyses were by Mr. G. Powell of this laboratory by using a Hewlett-Packard Model 185 CHN analyzer. [h] Melting points were recorded by using a Kofler "Thermospan" instrument and are corrected.

ring closure reaction has been recognized as the first step in racemization during peptide synthesis. The oxazolinone intermediate rapidly exchanges its proton on the C-4 position because the conjugate base has a planar aromatic structure.

We recently showed that phenol accelerates the degradation of 2-phenyloxazolin-5-one in aqueous buffer at about pH 8 and interpreted this result on a mechanism involving parallel hydrolysis of the oxazolinone and synthesis of phenyl hippurate. This observation, carried out spectrophotometrically, indicates that it should be possible to measure the formation of phenyl benzoylglycinates over a range of structures varying the substituent on the attacking phenol and on the 2-phenyl group of the oxazolinone. Since the rate constants for formation of oxazolinone from ester are available[3] or easily measured, we should be able to determine equilibrium constants for the oxazolinone formation and moreover study these as a function of structural change.

The change in equilibrium constant for a reaction as a function of a variation in structure is a necessary standard against which to measure the change in rate constant.[5] The results of such a comparison lead to an "index" of structure for the transition state relative to that of ground and product states.[6] Effective charges[7] may be calculated from the relative selectivities of rate and equilibrium constants. Previous work on structure reactivity relationships with aryl benzoylglycinates[3,8,9] is only able to compare the change in rate constant with the change in ionization equilibrium for the leaving phenol and is therefore not a valid index of transition-state structure.

Although the effect of structural change on equilibrium constants is an important parameter because of its use as a standard for transition-state structure, there is at present only a small body of accurate data. The reason for this lack of data is partly due to the difficulty in obtaining equilibrium constants for reactions of interest which are accurate enough to obtain reasonably accurate selectivities. Most equilibria markedly favor either products or reactants, and only one rate constant is conveniently measured. The system under discussion provides an excellent opportunity to measure accurate equilibrium constants for an acyl-group-transfer reaction.

Experimental Section

Materials. Substituted hippuric acids were prepared by reacting the corresponding benzoyl chloride with glycine under aqueous Schotten-Baumann conditions. The products were recrystallized from suitable solvents (see Table I) and the structures confirmed from the infrared and NMR spectra.

4-Nitrophenyl esters of substituted hippuric acids were prepared by reacting equimolar amounts of the substituted acid, 4-nitrophenol and dicyclohexylcarbodiimide in ethyl acetate containing approximately 10% pyridine. The mixture was stirred for 3 to 4 h and then filtered and the filtrate evaporated. Recrystallization of the residue from ethanol gave the ester in reasonable yield. The melting points and analyses are given in Table I; infrared and NMR spectra are consistent with those of the proposed structures.

The 2-aryloxazolin-5-ones were prepared by gently warming the substituted hippuric acid in acetic anhydride and evaporating the mixture in vacuo after all the acid had dissolved. The product oxazolinones were recrystallized, and the melting points and analyses are recorded in Table I; structures are confirmed by NMR and infrared spectroscopy.

Aryl esters of methanesulfonylglycine were from a previous study.[10] Deuterium oxide (99.7% D) and DCl in D_2O (99.0% D) was from Merck, Sharp and Dohme Ltd., Oxygen-18 enriched water (approximately 1.6 and 3.5% ^{18}O) was from Prochem. The ^{18}O-enriched NaOH was prepared by cautiously dissolving sodium metal in enriched water; ^{18}O-enriched HCl solution was prepared by passing the gas through enriched water. Both solutions were roughly 0.5 M as judged from microtitration. Ordinary water was doubly distilled from glass; buffers and reagents used in the kinetics were either of analytical reagent grade or were redistilled or recrystallized prior to use.

Methods. Nuclear magnetic resonance spectra were recorded by Dr. D. O. Smith with a JEOL 100-MHz instrument; infrared spectra were recorded on a Unicam SP 200 machine. Measurements of pH were carried out by using a Radiometer PHM 62 digital pH-meter standardized with E.I.L. buffers to ±0.02 pH units.

Kinetics were measured by using the following general technique; a small volume of the substrate (usually 25λ) dissolved in acetonitrile or alcohol solution was placed on the flattened tip of a glass rod and introduced into buffer containing the appropriate reagents (2.5 mL) in a silica cell in the thermostated cell compartment of a spectrophotometer

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(9) J. P. Morawiec and I. Z. Siemion, *Rocz. Chem.*, **51**, 1867 (1977).
(10) A. Williams, E. C. Lucas, and A. R. Rimmer, *J. Chem. Soc. (Perkin 2)*, 621 (1972).

Table II. Reaction of Hydroxide Ion with 4-Nitrophenyl-Substituted Benzoylglycinates[a]

substituent	$10^{-4}k_{OH}$/ M^{-1} s^{-1} [b,c]	N[d]	"K_{eq}"[e]
3-nitro	1.12	5	2.18
3-chloro	0.89	5	5.49
4-methyl	1.26	4	10.5
parent	1.26	4	6.33
4-chloro	1.12	5	4.89
4-methoxy	0.794	5	5.75
4-nitro	1.68	5	1.04

[a] 25 °C, ionic strength kept at 1 M with KCl, wavelength 400 nm. [b] pK_w = 13.97 at 1 M ionic strength (work of Dr. S. Thea). [c] pH range 6–12 using tris(hydroxymethyl)aminomethane (Tris), phosphate, carbonate, and hydroxide buffers. [d] Number of kinetic runs. [e] "K_{eq}" is the ratio of k_{OH}/k_2, where k_2 is the rate constant for attack of phenolate anion on the corresponding 2-phenyloxazolin-5-one (from Table VI). "K_{eq}" is not a true equilibrium constant. Since the selectivity of the 4-nitrophenyl ester to hydroxide attack is reasonably expected to be the same as for the phenyl esters the selectivity of "K_{eq}" should be that for the true equilibrium constant K_{eq}.

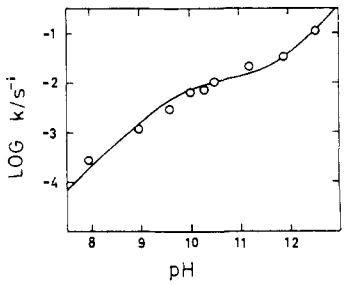


Figure 1. Dependence on pH of the hydrolysis of phenyl N-methanesulfonylglycinate. Conditions are as in Table III. The line is theoretical from eq 1 with the use of parameters from Table III.

(Perkin-Elmer Model 124 Unicam SP 800 or SP 500). The absorption was recorded as a function of time on a Servoscribe potentiometric recorder. First-order kinetics were measured by plotting $A_t - A_\infty$ vs. time (A_t = absorbance at time t) on two-cycle semilogarithmic graph paper.

The kinetics of the reaction of phenols with aryl oxazolinones was measured in the following way. A solution of the phenol in Tris (tris(hydroxymethyl)aminomethane, 0.05 M, 1 M ionic strength made up with KCl) was adjusted to a convenient pH in the range 7–9, and a solution of the same buffer without the phenol was adjusted to the same pH value. The phenol-containing buffer was diluted with the Tris buffer to obtain a series of phenol dilutions with constant Tris concentration and pH. The disappearance of the oxazolinone (measured at 260 nm by a decrease in absorbance) was recorded for these buffers by the kinetic technique described above.

Oxygen-18 incorporation experiments were carried out by dissolving the parent 2-phenyloxazolin-5-one (200 mg) portionwise in either enriched NaOH or HCl solution (1 M, 5 mL). The solution was kept until it was judged that reaction was complete ($t_{1/2}$ was computed from data in Table IV); the NaOH solution was then acidified with enriched HCl and the precipitated hippuric acid recrystallized from water. In the case of the acid hydrolysis the hippuric acid product precipitated from the reaction mixture directly. The products, hippuric acid control, and the enriched aqueous solutions were subjected to mass spectral analysis (AEI MS 902 high-resolution mass spectrograph) under the direction of Dr. R. B. Turner.

Results

The hydrolyses of 4-nitrophenyl-substituted benzoylglycinates exhibit good first-order kinetics over at least 90% of the total reaction, and the resultant pseudo-first-order rate constants are proportional to the hydroxide ion concentration. Values of the derived second-order rate constants for hydroxide attack are given in Table II.

The hydrolyses of substituted phenyl N-methanesulfonylglycinates also show good pseudo-first-order kinetics and the pH dependence (Figure 1) of the rate constants fits eq 1. The rate

$$k = (k_1 + k_{OH^-}[OH])/(1 + a_H/K_a) \quad (1)$$

Table III. Kinetic Parameters for the Hydrolysis of Substituted Phenyl N-Methanesulfonylglycinates[a,c]

substituent	pK_{app}	log k_1/s^{-1}	log k_{OH^-}/ M^{-1} s^{-1}	log k_{OH^0}/ M^{-1} s^{-1}	N[d]
parent	9.7	−2.0	2.3	0.5	9
4-chloro	9.9	−1.7	2.4	0.6	9
4-nitro[b]	9.8	−1.2	3.0	1.1	10
4-methyl	10.2	−1.9	1.9	0.2	8
4-methoxy	9.8	−2.1	2.1	0.2	8
3-nitro	9.6	−1.4	3.0	1.2	9

[a] 25 °C, ionic strength maintained at 1 M with KCl. [b] Buffer effect tested with Tris at pH 9.00 for Tris/M ($10^3k/s^{-1}$): 1.0 (25.6); 0.5 (17.4); 0.1 (6.56); 0.05 (5.02); 0.01 (4.26); 0 (4.4). [c] Buffers kept at 0.05 M, pH range 7–13, phosphate, Tris, carbonate, and hydroxide. [d] Data points.

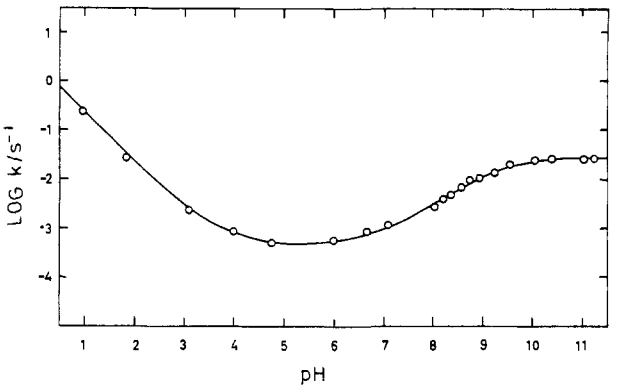


Figure 2. Dependence on pH of the hydrolysis of 2-(4′-chlorophenyl)-oxazolin-5-one; conditions as in Table IV. The line is theoretical from eq 2 with the use of parameters from Table IV.

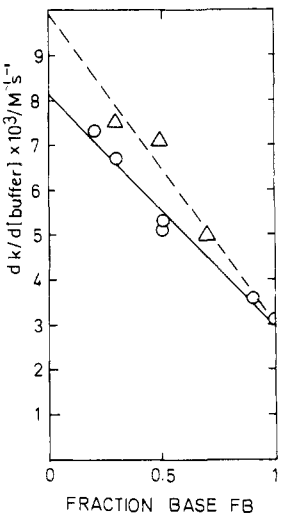


Figure 3. Degradation of 2-phenyloxazolin-5-one in acetate buffers. Circles are for water and triangles for deuterium oxide solvents. Lines are theoretical with the use of parameters in the Results section and from Table V.

data were fitted to eq 1 by using a grid search method and a computer. The results for pK_a and k_{OH^-} are recorded in Table III, together with the bimolecular rate constant k_{OH^0} for the attack of hydroxide ion on the neutral ester ($k_{OH^0} = k_1K_a/K_w$).

The hydrolysis of 2-aryloxazolin-5-ones was measured over a pH range from 1–13 (see for example Figure 2). The kinetics obey good first-order rate laws, and the pseudo-first-order rate constants fit eq 2. The kinetic parameters are collected in Table

$$k = k_Ha_H + k_{H_2O} + k_{lim}/(1 + a_H/K_a) \quad (2)$$

IV; the parameter k_{lim} is a composite rate constant comprising the parameter k_{OH}, the bimolecular rate constant for attack of hydroxide ion on the neutral oxaozlinone, and is given by the

Table IV. Hydrolysis of 2-Aryloxazolin-5-ones[a]

substituent	λ^d	N^c	$k_H/M^{-1}\ s^{-1}$	$10^4 k_{H_2O}/s^{-1}$	$10^2 k_{lim}/s^{-1}$	$10^3 k_{OH}{}^b/M^{-1}\ s^{-1}$	pK_a
3-nitrophenyl	310	17	0.794	7.54	1.00	5.13	8.25
3-chlorophenyl	245	23	1.70	7.08	1.78	1.62	9.00
4-methylphenyl	260	35	6.31[e]	4.83	5.62	1.20	9.63
phenyl	260	28	4.79	6.31	5.48	1.99	9.40
4-chlorophenyl	260	20	2.24	5.01	2.82	2.29	9.05
4-methoxyphenyl	275	26	15.8	4.10	10.0	1.38	9.82
4-nitrophenyl	450	18	0.501	7.41	0.316	16.2	7.25

[a] 25 °C, ionic strength maintained at 1 M with KCl. [b] $k_{OH} = k_{lim}K_aK_w$; $pK_w = 13.97$. [c] Data points. [d] Wavelength used for kinetics (nm); the wavelength was varied according to the pH. [e] The rate constant is linear in hydrogen ion concentration up to 1 M HCl for this oxazolinone.

Table V. Reaction of Oxyanions with 2-Phenyloxazolin-5-one[a]

nucleophile	$K_{eq}{}^e$	N^d	pH[b]	$k^c/M^{-1}\ s^{-1}$	FP[g]	FO[h]	$k_2/M^{-1}\ s^{-1}$
			Phenolate Anion				
4-methoxy	2.18×10^{-2}	6	8.55	34	0.0219	0.880	1800
4-methyl	9.73×10^{-3}	6	8.60	24	0.025	0.863	1100
parent		6	8.20	15.5	0.0175	0.941	940
	3.63×10^{-2}	6	8.63	37	0.0457	0.855	930
		10	9.20	88.1	0.151	0.613	930
4-chloro	0.413	8	8.62	60	0.148	0.858	470
3-ethoxycarbonyl		5	8.62	120	0.261	0.858	550
3-chloro	1.15	6	8.60	80	0.275	0.863	340
2-chloro		11	8.65	46	0.608	0.852	89
3-nitro	51.3	7	8.57	17	0.624	0.871	31
4-ethoxycarbonyl		12	8.66	41	0.591	0.846	81
hydroxide ion[f]							1990
water							6.31×10^{-4} [i]
acetate ion		28					3.00×10^{-3}
		(9)[j]					(3.00×10^{-3})[i]
azide ion	942[k]	4	8.35	14.3		0.918	15.6

[a] 25 °C, ionic strength maintained at 1 M with KCl, 260 nm, oxazolinone concentration approximately 10^{-4} M, phenol concentration in the range 5–20 $\times 10^{-4}$ M. [b] The pH is an average of the observed values which differed by no more than ±0.01 units. [c] Slope of the rate constant versus total phenol concentration. [d] Number of data points. [e] $K_{eq} = k_{OH}/k_2$, where k_{OH} is derived from ref 3. [f] The pK_a of water is taken to be 16.5 (C. K. Sauers, W. P. Jencks, and S. Groh, *J. Am. Chem. Soc.*, 97, 5546 (1975)). [g] FP = fraction of phenol present as the phenolate anion. FP is obtained by using pK_a^{ArOH} and the pH. [h] FO = fraction of the 2-phenyloxazolinone present as the neutral species. FO is obtained by using the pK_a from Table IV. [i] Units are s^{-1}. [j] Value for deuterium oxide solvent. [k] Determined as in footnote *e* by using k_{OH} from ref 3.

equation $k_{lim} = k_{OH}K_w/K_a$; values for k_{OH} are also presented in Table IV. Terms due to attack of hydroxide ion on the ionized oxazolinone were not observed.

Reactions of 2-phenyloxazolin-5-ones in Tris buffers with increasing phenol concentration give first-order kinetics which obey eq 3, where FO is the fraction of the oxazolinone present in the

$$k = k_0 + k_2[\text{phenolate anion}]\text{FO} \quad (3)$$

neutral form at the pH in question. The quantity k_0 is the sum of spontaneous hydrolysis and the reaction of the oxazolinone with the buffer. At the pH values in question the hydrolysis of the synthesized phenol aroylglycinate is negligible over the time for the decomposition of the phenyloxazolinones; the hydrolysis rate constant may be calculated from the hydrolysis data for the corresponding 4-nitrophenyl aroylglycinate by assuming a Brønsted β_{LG} of −0.8 for variation of the substituent in the phenol-leaving group.[3] The concentrations of the phenyloxazolinones were such that their decomposition in the presence of the phenols was pseudo-first order (oxazolinones at 10^{-4} M and phenols at 0.5–2 $\times 10^{-3}$ M). The value of k_2 in eq 3 was estimated from the slope of the plot of k_{obsd} vs. total phenol concentration by division by the fraction of un-ionized phenyloxazolinone (FO) and phenolate anion (FP). The latter values were obtained for the pH in question from the appropriate pK_a values (Tables IV, V, and VI) and eq 4.

$$K_a = a_H[A^-]/[HA] \quad (4)$$

In the case of phenol reacting with 2-phenyloxazolin-5-one three different pH values were employed and the constancy of the estimated value of the bimolecular rate constant assuming reaction between the phenolate anion and neutral oxazolinone indicates that reaction is either phenolate with neutral oxazolinone or phenol with anionic oxazolinone. No terms in phenol and neutral oxazolinone or phenolate anion and oxazolinone anion are apparent from the kinetics. The data for the reaction of nucleophiles with oxazolinones are collected in Tables V and VI.

Table VI. Reaction of Phenoxide Ion with 2-Aryloxazolin-5-ones[a]

aryl group	λ^h	N^b	pH[c]	$k^d/M^{-1}\ s^{-1}$	FP[e]	FO[f]	$k_2/M^{-1}\ s^{-1}$
3-nitrophenyl	350	6	8.62	36	0.0447	0.299	3290
3-chlorophenyl	245	7	7.95	23.7	0.0099	0.918	2610
4-methylphenyl	260	8	8.01	8.6	0.0114	0.977	772
phenyl	260	22					930[g]
4-chlorophenyl	260	11	8.15	8.6	0.0156	0.900	613
4-methoxyphenyl	275	8	7.95	6.8	0.0099	0.987	696
4-nitrophenyl	450	8	8.58	17.8	0.0409	0.0447	9740

[a] 25 °C, ionic strength made up to 1 M with KCl. [b] Data points. [c] Average pH (values did not differ by more than ±0.01 units). [d] Slope of the rate constant vs. total phenol concentrations. [e] Fraction of phenolate ion present calculated from $pK_a = 9.95$ and the pH. [f] Fraction of neutral oxazolinone calculated from the pK_a's given in Table IV. [g] See Table V.

The rate constant for the reaction of phenol with anionic 2-phenyloxazolin-5-one may be calculated from k_2 (Table V) and the pK's of the phenol and oxazolinone; the value ($930 \times 10^{-9.95}/10^{-9.4} = 262\ M^{-1}\ s^{-1}$) is over 50 000-fold larger than that for attack of hydroxide ion on the oxazolinone anion (we are only able to estimate an upper limit for the latter value $< 5 \times 10^{-3}\ M^{-1}\ s^{-1}$), thus eliminating the kinetic ambiguity.

Product analysis studies were carried out on the reaction of 2-phenyloxazolin-5-one with 3-nitrophenol. 3-Nitrophenol has the advantage that its change in concentration may be followed

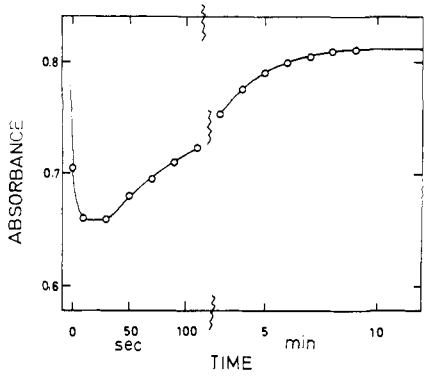


Figure 4. Degradation of 2-phenyloxazolin-5-one (9.89×10^{-4} M) in Tris buffer (0.05 M, pH 9.08, 1 M ionic strength, 25 °C) containing 3-nitrophenol (2.54×10^{-3} M) monitored at 465 nm. A control experiment with no 3-nitrophenol gave no change in absorbance at 465 nm.

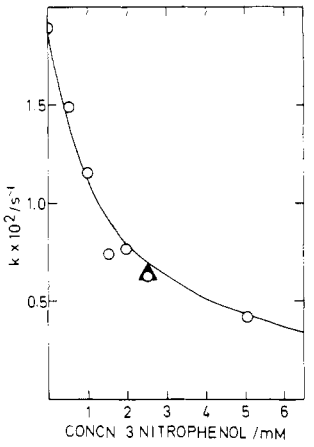


Figure 5. Dependence on 3-nitrophenol concentration of the hydrolysis of 3-nitrophenol hippurate (circles). The line is theoretical from eq 5 with the use of parameters given in the text. The triangle is the rate constant for the *second phase* of the degradation of 2-phenyloxazolin-5-one in 3-nitrophenol-containing buffers. Conditions: Tris at 0.05 M, 1 M ionic strength, 25 °C, pH 9.08, 3-nitrophenyl hippurate at 1.08×10^{-3} M.

at high wavelengths (>450 nm) where absorbance changes due to the disappearance of parent oxazolinone are not monitored. Addition of the oxazolinone (9.89×10^{-4} M) to a Tris buffer containing 3-nitrophenol (2.54×10^{-3} M) at pH 9.08 was monitored in the visible spectrum at 465 nm. A rapid decrease in absorbance was observed due to the consumption of 3-nitrophenol; a later, slower, increase in absorbance had a first-order rate constant (Figure 4) which was identical with that for decomposition of 3-nitrophenyl hippurate (see Figure 5) in the same buffer in the absence of added phenyloxazolinone.

A further experiment confirming the overall mechanism involved observing the rate constant for hydrolysis of 3-nitrophenyl hippurate in Tris buffer (pH 9.08) in the presence of increasing amounts of 3-nitrophenol (Figure 5). The pseudo-first-order rate constants decreased exponentially with 3-nitrophenol concentration and obeyed eq 5, where k_F is the rate constant for formation of

$$k = \frac{k_F k_D}{(k_2[\mathrm{MNP}]\mathrm{FO} + k_D)} \qquad (5)$$

oxazolinone from the 3-nitrophenol hippurate ester in the solution (1.89×10^{-2} s^{-1}), k_D is the rate constant for the decomposition of the oxazolinone under the conditions of the experiment in the absence of added 3-nitrophenol (3.03×10^{-2} s^{-1}), k_2 is the bimolecular rate constant for attack of 3-nitrophenolate anion on 2-phenyloxazolin-5-one (see Table V), and [MNP] is the concentration of 3-nitrophenolate anion.

The decomposition of 2-phenyloxazolin-5-one in acetate buffers was found to obey first-order kinetics; the rate constants up to 1 M total buffer concentration are linearly dependent on concentration of buffer. The slope of the rate constant vs. buffer concentration is linearly dependent on the fraction of base (Figure 3), and both acid and base species of the acetate buffers are reactive (eq 6). The value of k_{Acid} is 8.2×10^{-3} M^{-1} s^{-1} and k_2

$$k = k_{bkgd} + k_{Acid}[\mathrm{Acid}] + k_2[\mathrm{Base}] \qquad (6)$$

is recorded in Table V; k_{bkgd} is dependent on pH (see Table IV). The deuterium oxide solvent isotope effect on the catalysis was determined at FB = 0.3, 0.5, and 0.7; the data are subject to more error than in the protio experiments, and the results are that within the experimental error there is no deuterium oxide solvent isotope effect on the catalysis by acetate (k_2). The value of k_{DOAc} obtained from the fraction of base plot (Figure 3) is 9.8×10^{-3} M^{-1} s^{-1}, leading to an inverse solvent isotope effect of 1.20.

Brønsted or Hammett parameters for the variation of equilibrium or rate constant with substituent were determined from logarithmic plots vs. the pK_a of the appropriate phenol or the σ or σ^- value. The plots were linear with good correlation coefficients (except for those plots with low slopes), and the data are collected in Table VII. The plot of log k_2 vs. the pK_a of the attacking nucleophile is illustrated in Figure 6.

Position of Bond Cleavage in Oxazolinone Hydrolysis. The mass spectrum of hippuric acid has major peaks at m/e 179 (M^+), 135 ($M - CO_2^+$), 105 ($C_6H_5CO^+$), and 77 ($C_6H_5^+$). We are therefore able to determine the position of attack on 2-phenyloxazolin-5-one

Table VII. Collection of Brønsted and Hammett Equations Governing the Rates and Equilibria of the Oxazolinone Reactions

reaction	slope[c]	intercept[a]	r/%[d]
2-Aryloxazolin-5-ones			
k_H	-1.25ρ	0.70	98.3
k_{OH}	$0.70\rho^-$	3.22	94.6
k_{H_2O}	0.16ρ	−3.30	80.4
k_{lim}	$-1.20\rho^-$	−1.33	96.2
k_2 (PhO^- attack)	$0.77\rho^-$	2.97	93.0
K_a	$-1.64\rho^-$	9.42	99.8
"K_{eq}"[b]	-0.71ρ	0.79	87.1
2-Phenyloxazolin-5-one with Aryloxide Ion			
k_2 (ArO^- attack)	0.76β	−4.49	94.0
K_{eq}	-1.86β	17.1	99.1
Aryl *N*-Methanesulfonylglycinate			
K_a	-0.067β	−9.21	40.1
k_{OH}^- (anion + OH^-)	-0.32β	3.58	90.9
k_{OH}° (neutral + OH^-)	-0.35β	5.64	92.8
4-Nitrophenyl Aroylglycinates			
k_{OH}	0.12ρ	0.02	48.0

[a] The intercept is quoted as the logarithm (base 10) of the parameter measured. [b] See Table II, footnote *e*. [c] The logarithm (base 10) of the parameter is correlated with pK_a, σ or σ^-. [d] The correlation coefficient for the low slopes is poor. Perusal of the graph in these cases is a better guide to the correlation obtained. We believe that the slope is essentially zero in these cases.

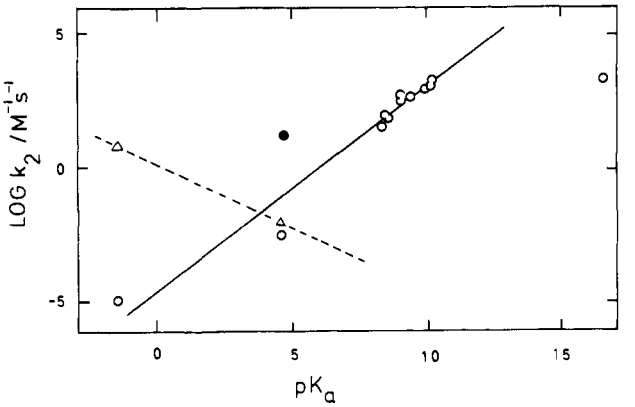
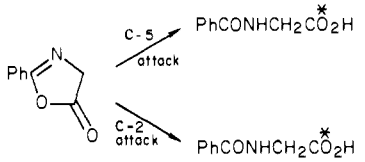


Figure 6. Brønsted dependence of k_2 for oxyanion attack on 2-phenyloxazolin-5-one (circles). Triangles represent acid-catalyzed rate constants; the filled circle is k_2 for the azide ion. Lines are theoretical from text and Table VII.

Scheme I



by water to yield hippuric acid under acid or alkaline conditions. Oxygen-18 enriched water should give enrichment of the 107 mass peak for attack at C-2; in both acid and alkaline hydrolyses the enrichment was indistinguishable from that for the natural hippuric acid, indicating attack at C-5 (see Scheme I). The enrichment of the water in the acid experiment was 1.79% $^{18}O/^{16}O$ which leads to an enrichment of the 107 mass of 2.05% by assuming complete attack at C-2. The observed enrichment (0.50%) is, within experimental error, identical with the natural enrichment of the 107 mass peak (0.47%). The alkaline experiment had water with an enrichment of 3.51% for $^{18}O/^{16}O$, leading to a calculated enrichment of the 107 mass peak of 3.78% for complete attack at C-2. The observed enrichment (0.45%) is within experimental accuracy the same as that of natural phenacylium ion. The calculations of the enrichments were made by assuming the published[11a] natural abundances of ^{13}C, ^{17}O, ^{18}O, ^{15}N, and ^{2}H.

Discussion

There is little doubt in the literature that the decomposition of aryl hippurates in aqueous base proceeds via an oxazolinone intermediate.[1-3] In order to obtain the equilibrium constant for the reaction, we must be sure that the synthesis is measured by the accelerated decomposition of oxazolinones in buffers containing phenols. Williams and Young[4] showed by the use of infrared spectroscopy that in chloroform solution the equilibrium between oxazolinone, phenol, and *N*-aroylaminoacid phenyl ester was set up rapidly (oxazolinone–ester = 0.6:1 in the equilibrium mixture). Two pieces of evidence indicate that in aqueous solution a similar equilibrium exists. The hydrolysis of 3-nitrophenyl hippurate in buffered solutions is retarded by increasing concentrations of 3-nitrophenol in a classical type "mass law" experiment.[11b] We show that there is very good agreement between the values of rate constant calculated for the decomposition by using the data of Table V and the observed values (Figure 5). The reaction of 2-phenyloxazolin-5-one in buffers containing 3-nitrophenol at the same pH as in the "mass law" experiment is characterized by an initial drop in absorbance (Figure 4) due to the disappearance of a fraction of the 3-nitrophenol (at 465 nm); the decrease in absorbance is followed by an increase which obeys a first-order rate law. The pseudo-first-order rate constant for this increase in absorbance is closely similar to that for the decomposition of 3-nitrophenyl hippurate in the buffer which contains the same 3-nitrophenol concentration (Figure 5). Both pieces of evidence give us complete confidence in our own interpretation of the kinetics in the experiments synthesizing ester from oxazolinone and thus provide fresh evidence for the oxazolinone mechanism for aryl hippurate hydrolyses.

Linear Free-Energy Relationships for Phenolate Anion Attack. The Brønsted β values for the rate and equilibrium constants for variation of the phenolate ion leaving group are illustrated in Figure 7 together with the effective charges for the aryl oxygen atom in ground and transition states. The effective charge on the ester oxygen is slightly more positive than that on simple aliphatic esters, and this might be due to the electron-withdrawing ability of the amino group; ionizing the amido group reduces the effective charge from +0.86 to +0.79 in accord with an expected reduction in electropositivity. The very large β_{LG} observed previously for hydroxide attack is seen to reside largely in the decomposition of the anionic species; the magnitude of β_{LG} while large does not imply a very late transition state because the change in effective

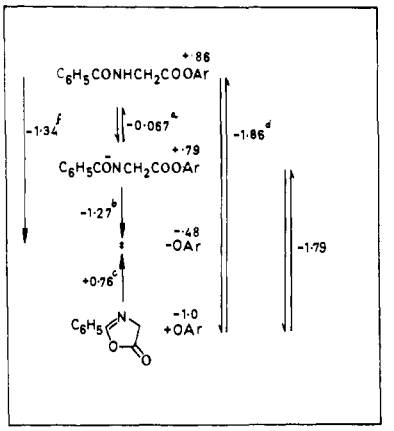


Figure 7. Selectivity of the oxazolinone reaction to change in the substituents on the leaving phenol: (a) log K_a vs. pK_a of ArOH (β_{K_a}); (b) −1.34 − (−0.067) ($\beta_{k_{-2}}$); (c) log k_2 vs. pK_a of ArOH (β_{k_2}); (d) log K_{EQ} vs. pK_a of ArOH ($\beta_{K_{EQ}}$); (e) log K vs. pK_a of ArOH (β_K) ($K_{EQ} = KK_a/K_w$). The value of β_K should also equal the difference between $\beta_{k_{-2}}$ and β_{k_2}, and the discrepancy between the two values is due to the imperfect correlations on each rate constant.

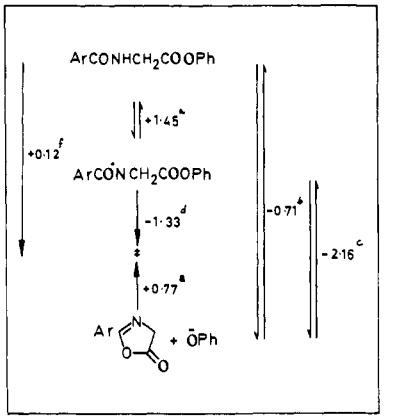


Figure 8. Selectivity of the oxazolinone reaction to change in the substituents on the 2-phenyl groups: (a) log K_a vs. σ (ρ_{K_a}) (this is an average of the values obtained by K. T. Douglas and A. Williams, *J. Chem. Soc., Perkin Trans. 2*, 2112 (1975)); (b) log K_{EQ} vs. σ ($\rho_{K_{EQ}}$); (c) log K vs. σ (ρ_K) (see part e of Figure 7 for comments on the discrepancy between ρ_K and the value obtained from $\rho_{k_{-2}}$ and ρ_{k_2}); (d) 0.12–1.45 ($-\rho_{k_{-2}}$); (e) log k_2 vs. σ^- (ρ_{k_2}); (f) log k_{OH} vs. σ ($\rho_{k_{OH}}$).

charge of −1.11 is only 0.62 of the difference in effective charge between anionic substrate and oxazolinone and phenolate anion. The effective charge is defined by eq 7 and 8. The effective charge on the phenolate oxygen in the product state (E_{ps}) is −1.0 and the charges on the oxygen in the ground and product states of phenol ionization are defined as zero and −1, respectively.

$$E_{ts} = E_{gs} + \beta_F\beta_{EQ}/(\beta_F - \beta_R) \quad (7)$$

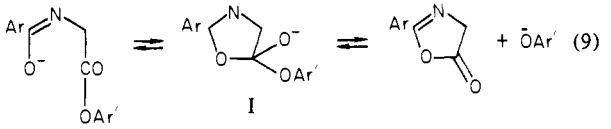
$$E_{gs} = E_{ps} - \beta_{EQ} \quad (8)$$

The effect of varying the substituent on the 2-phenyl group of the oxazolinone is treated by using the Hammett ρ approach because there is no appropriate model such as phenol ionization to define an effective charge. The ρ values are illustrated in Figure 8, and we assume with little reason for doubt that the ρ for alkaline hydrolysis of the phenyl ester is the same as that for the 4-nitrophenyl ester.[12] It is not possible to calculate an effective charge for the attacking oxygen which will be comparable with that on the exocyclic oxygen, but the forward rate constant is 0.63 as selective as the overall equilibrium constant (conjugate base to oxazolinone) toward a change in substituent on the 2-phenyl group.

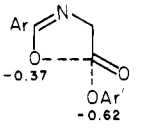
(11) (a) R. C. Weast, Ed., "The Handbook of Chemistry and Physics", 51st ed., CRC Press, Cleveland, Ohio, 1970. (b) W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.*, **90**, 2622 (1968).

(12) J. F. Kirsch, W. Clewell, and A. Simon, *J. Org. Chem.*, **33**, 127 (1968).

Speculation on the Mechanism of the Reaction of Oxazolinone with Phenolate Ion. A possible mechanism for the oxazolinone reaction involves a stepwise mechanism (eq 9), and the rate-limiting step should be the intramolecular attack of the amido oxyanion on the ester function; the return step is expected to be less than the forward (for the decomposition of the intermediate) because both involve cleavage of oxygen–carbon links and the phenolate-leaving group is the least basic. Moreover, the forward step is favored by a gain in translational and rotational entropy whereas the return (an intramolecular reaction) is not.[13] If we use the ratio $\alpha = \beta_F/\beta_{EQ}$[6] as a transition-state index (relative to the structure of ground and product states), then the value of 0.63 measured from the variation of the 2-phenyl substituent is consistent with 63% of bond formation going from amide anion to oxazolinone in agreement with a stepwise and concerted scheme; the transition-state index of 0.62 for cleavage of the exocyclic C–O bond is not however consistent with the stepwise process because this should result in little exocyclic cleavage in the transition state of the rate-limiting step.

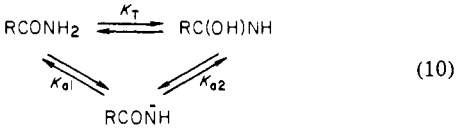


There is an apparent "additivity" in the transition-state indices in that the advancement of C–OAr bond cleavage is balanced by that of endocyclic bond formation (II). This result is consistent with a concerted reaction.



II

The pK_a of the leaving amido oxyanion in the return to ester from the intermediate (I) in eq 9 is not directly measureable but may be estimated from the thermodynamic cycle in eq 10. The



(10)

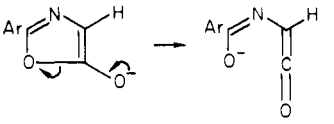
value of K_T has been estimated for acetamide[14] to be 10^{-8} and the pK_{a1} for benzamide to be 19 from studies with 2-propanol solvent.[15,16] It is expected that K_T for benzamide should be larger than that for acetamide due to the greater electron-attracting power of the aromatic ring. The pK_{a2} for isobenzamide is thus greater than 11 and the pK_a of the phenols studied here. Nevertheless, if the forward decomposition of I were rate limiting due to a more strongly basic phenolate leaving group, we might expect a higher transition-state index than the one observed (63%).

The concerted mechanism cannot involve a linear disposition of nucleophile, leaving group, and central carbon atoms in the transition state owing to steric constraints; we envisage a nonlinear structure where nucleophile enters essentially at right angles to the departing leaving atom.

Reaction of Hydroxide Ion with Oxazolinones. The alkaline region of the pH dependence of the hydrolysis of 2-aryloxazolin-5-ones has a sigmoidal form which could derive from direct attack of hydroxide ion on a neutral species which ionizes to yield unreactive anion, decomposition of a reactive anion which is unreactive in its conjugate acid form, or a mixture of both the former mechanisms. The alkaline hydrolysis occurs through attack at the C-5 carbon as indicated from the oxygen-18 enriched water studies.

Simple stepwise attack of hydroxide ion on the carbonyl group in the neutral species (similar to eq 9) through an intermediate should not give the observed Hammett σ^- dependence because the departure of hydroxide ion in the return step should be slower than that of the isoamide oxyanion and the transition state of the rate-limiting step should therefore involve no endocyclic bond cleavage. The Hammett σ^- dependence is consistent with endocyclic C–O bond cleavage in the transition state of a concerted displacement.

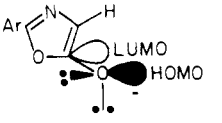
An E1cB type process consistent with the Hammett sigma-minus dependence (eq 11) may be excluded by using data from



(11)

Jersey and Zerner,[2] who investigated the hydrolysis of 2-phenyloxazolin-5-ones substituted at the 4-position. At pH 8.1, where all substrates are present essentially as the neutral form, the relative rate constants for hydrolysis are 8.8:5.3:1 for 4-methyl, unsubstituted, and 4,4-dimethyl, respectively. In the region of pH employed the rate constants are proportional to k_{OH}, the second-order rate constant for reaction of hydroxide ion with the neutral species. We may estimate the relative rate constants, assuming that there is little electronic effect of the substituents, from the Taft E_s values[17] (and making the reasonable assumption that δ is the same as in hydroxide ion attack on carboxylic esters); the ratio 11.7:29.5:1 is obtained, and it is seen that the parent oxazolinone reacts more slowly than expected by assuming the nucleophilic mechanism which must occur with the 4,4-dimethyl species. A change in mechanism to E1cB would require a faster rate constant.

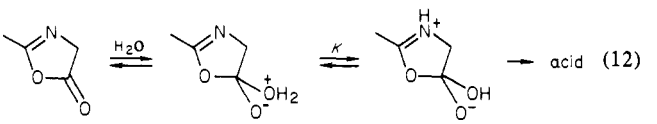
The elimination mechanism is not however excluded on steric grounds because an orbital on the oxygen containing a lone pair is of the correct symmetry to overlap with the unoccupied orbital antibonding to the cleaving σ bond (III). It is interesting that



III

although the E1cB mechanism is not excluded stereoelectronically, all the known E1cB reactions of acyl group transfer possess *two* occupied orbitals antiperiplanar to the leaving bond. The work of Deslongchamps[18a] indicates that elimination from tetrahedral carbon to acyl carbon also utilizes two antiperiplanar filled orbitals; presumably these *two* electron pairs provide the driving force which is not required in the formation of aldehydes and ketones from acetals where only one antiperiplanar lone pair is available.[18b]

Water Attack on Oxazolinones. The slightly positive ρ value for the rate constant for water attack (k_{H_2O}) for the hydrolysis of 2-aryloxazolin-5-ones indicates that attack must be at a center not coupled directly to the substituent. We discard the possibility that hydroxide attacks the protonated oxazolinone because this requires a rate constant in excess of 6×10^{10} M^{-1} s^{-1} for the phenyloxazolinone; the pK_a of the oxazolinone is known to be less than zero (see footnote e of Table IV). A possible stepwise mechanism involves water attack on the carbonyl oxygen (eq 12),



(12)

and in order for the reaction to proceed the initial intermediate must transfer the proton from the attacking oxygen to nitrogen;

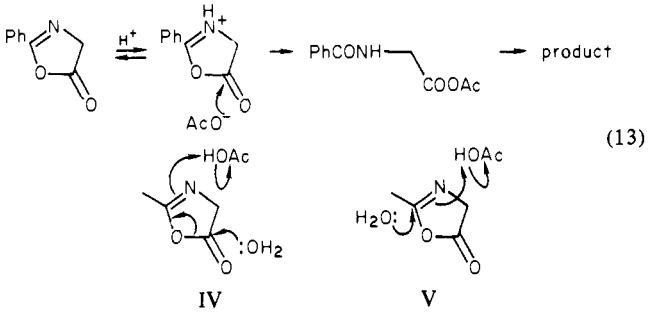
(13) M. I. Page, *Chem. Soc. Rev.*, **2**, 295 (1973).
(14) A. R. Fersht, *J. Am. Chem. Soc.*, **93**, 3504 (1971).
(15) J. Hine and M. Hine, *J. Am. Chem. Soc.*, **74**, 5266 (1952).
(16) K. Bowden, *Chem. Rev.*, **66**, 119 (1966).
(17) T. H. Lowry and K. S. Richardson, "Mechanism and Theory in Organic Chemistry", Harper and Row, New York, 1976, p 68.
(18) (a) P. Deslongchamps, *Tetrahedron*, **31**, 2463 (1975); (b) A. J. Kirby and R. J. Martin, *J. Chem. Soc., Chem. Commun.*, 803 (1978).

this equilibrium constant is estimated to be approximately unity because the oxazolinone nitrogen has a $pK_a \geq 0$ and that of an alcohol is about −2.[19] The return rate constant from initial intermediate to reactants is very large because water is an exceptionally powerful leaving group, and the decomposition of the final intermediate is therefore expected to be rate limiting; the mechanism is therefore consistent with a σ^- relationship. The presence or absence of a Hammett σ^- relationship is not easily detected for a low selectivity so that it is not possible in this case to exclude the stepwise mechanism; the water nucleophile is weaker than the hydroxide ion, but the lower selectivity observed for the former is not consistent with an expected later transition state and it is conceivable that different mechanisms operate for the two nucleophiles in this reaction.

Acid Catalysis

Acetate Buffer Catalysis. The degradation of 2-phenyloxazolin-5-one in acetate buffers exhibits a dependence on both acid and base forms of the buffer. The base has a bimolecular rate constant which fits the Brønsted relationship for reaction of phenolate anions with the oxazolinone (Figure 6). This result, coupled with the low deuterium oxide solvent isotope effect for the acetate parameter, indicates the reaction involves nucleophilic attack at the carbonyl center.

The general-acid term has an inverse deuterium oxide solvent isotope effect which indicates that the mechanism is specific acid–nucleophilic (eq 13) rather than true general-acid catalysis



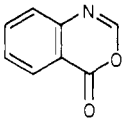
(13)

IV V

involving rate-limiting proton transfer (IV and V). The acid-catalyzed term combined with that for oxonium ion catalysis leads to a Brønsted selectivity of approximately 0.25 (see Figure 6) and perusal of Figure 6 indicates that general-acid terms relating to phenol would not be observable under the conditions employed to measure the basic reactivity of these nucleophiles. This is confirmed by experiments with phenol at different fractions of base (Table V) where any acid terms must be smaller than the error on an intercept at the fraction of base equal to zero.

Oxonium Ion Catalysis. The acid term k_H is reasonably assumed to stem from protonation on nitrogen followed by attack of water on the conjugate acid; the water is known from oxygen-18 enriched water studies to attack the carbonyl carbon rather than the imino function. Protonation on the carbonyl oxygen is excluded because alkyl esters have much lower acid hydrolysis rate constants than the ones observed here (for example, methyl acetate at 25 °C has 1.06×10^{-4} M^{-1} s^{-1}).[20] The observation of a Hammett ρ value of −1.25 is consistent with the proposed mechanism; protonation of the imino nitrogen would be expected to possess a Hammett selectivity close to −1, and water attack on the carbonyl oxygen is known to be insensitive to substituents on the 2-phenyl group. There is no evidence to enable us to distinguish between concerted or stepwise water addition.

There is a difference in position of attack by water on the present 2-phenyloxazolin-5-ones and the related 3,1-benzoxazin-4-ones[21a] in acid media; the latter species undergo attack at the imino carbon[21a] as in structure VI. The greater reactivity of the imino carbon in (VI) compared with that in the corresponding oxazolinone may result from the more weakly basic nitrogen attached to the aromatic nucleus.



VI

Peptide Synthesis. It is reasonable that all oxyanion leaving groups in activated aroylamino acid esters should fit the same Brønsted relationship for the equilibrium with oxazolinone and oxyanion; thus we expect the most basic leaving groups to yield the least oxazolinone by equilibrium (Table VII) and therefore to provide the least racemization. The reactivity of the esters to nucleophilic attack decreases with increasing basicity of the leaving group, and for amine attack as in peptide synthesis Satterthwait and Jencks summarize the Brønsted values ($\beta_{LG} = -0.6$ to -1).[21b] These values are much greater than the selectivity for oxazolinone formation ($\beta_{LG} = -1.34$)[3], and the latter reaction can never become more efficient as the basicity of the leaving oxyanion increases.

The formation of oxazolinone from hippuryl azide has an equilibrium constant (942, Table V) some 5 orders of magnitude lower than expected (2.1×10^8, see Table VII) for that of a hippurate ester with alcohol of similar pK_a; we suggest that part of the optical efficiency of the azide method of peptide synthesis over those methods involving oxygen-leaving groups is due to the relatively low equilibrium constant for oxazolinone formation. The small equilibrium constant results from both a low rate constant for decomposition of the azide and a high rate constant for reaction of azide ion with oxazolinone. The latter enhancement is related to the well-known "α-effect". In addition to these considerations another factor must be added to Young's original hypothesis.[22] Competition between the return of oxazolinone to acylamino acid derivative and the removal of a proton from C-4 of the oxazolinone will also affect the optical purity of the final peptide. Proton removal is not a function of phenolate anion concentration so that at a given pH the return to ester and hence optical efficiency depends on the reactivity of the phenolate anion. At a pH where the phenol is completely ionized the esters of the least acidic phenols will be the most optically efficient. At lower pHs the value of β_N (0.76) for phenolate anion attack (Table VII) ensures that the esters of the more acidic phenols have a small edge over the least acidic ones in aqueous solution.

The higher reactivity of the azide ion relative to oxyanions of similar basicity and of the relatively poor leaving ability of the azide ion appear to be common to other systems; it should also be noted that these do not involve cyclizations. Johnson and Rumon[23] find that azide is some 3 orders of magnitude more reactive than acetate ion (of similar pK_a) toward *N'*-(*N*,*N*-dimethylcarbamoyl)pyridinium ion. Azide ion is found to be 2 orders of magnitude more reactive than an oxyanion of similar basicity to attack on isocyanic acid[24,25] and toward 4-nitrophenyl acetate the ratio is 3 orders of magnitude.[26] The expulsion of azide ion from phenylmethanesulfonyl azide is about 10^5-fold slower than the expulsion of an oxyanion of similar basicity from the corresponding sulfonyl derivative.[27] The equilibrium constant for isocyanic acid formation from carbamoyl azide is approximately $10^{5.5}$-fold less favorable than that from the carbamate ester of an alcohol of $pK_a = 4.7$.[24,25]

Ionization of the Carbon Acid. The 2-substituted phenyloxazolin-5-ones have pK_a's in the range 7–10 which obey a Hammett σ^- correlation ($\rho^- = -1.65$). This relationship is con-

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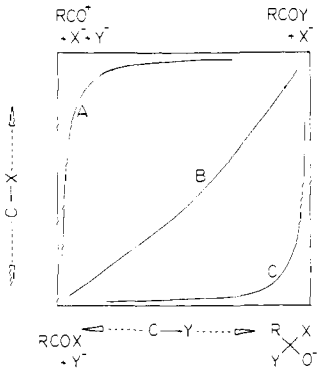


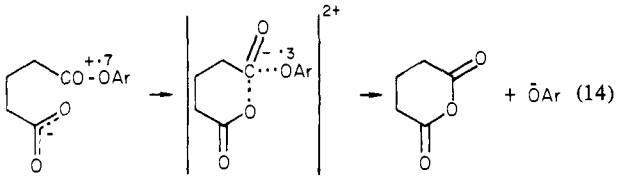
Figure 9. Potential energy surface for the displacement of a leaving group X^- from an acyl derivative by a nucleophile Y^-. Energy coordinate is vertical from the plane of the paper, and the contours are omitted for clarity. Pathway A represents a mechanism with S_N1 timing; pathway B is a concerted mechanism; pathway C represents the addition–elimination timing.

sistent with a carbanion derived from C-4 with charge spread over the aromatic five-membered ring *and* the aromatic ring of the C-2 substituent.

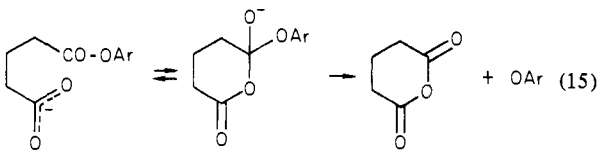
Alkaline hydrolysis of the conjugate base of the oxazolinone is not observed; the rate constant in the case of the 2-phenyloxazolinone ($<5 \times 10^{-3}$ M^{-1} s^{-1}) is approximately 4×10^5-fold slower than that of attack on the neutral ester assuming an increase of 10% was easily noticed in the value of k_{lim} at 1 M KOH. This value is extraordinarily low for an electrostatic effect, and we attribute it to the aromatic nature of the conjugate base compared with the neutral heterocycle. It is noted that unsaturated oxazolinones with an exocyclic double bond at the 2-position are much more stable to hydrolysis than the saturated oxazolinone due probably to the aromatic character of the former.

Concerted Mechanisms of Acyl-Group Transfer. Following Bender's discovery of isotopic exchange at the carbonyl oxygen during the hydrolysis of esters in aqueous solution,[28] there have been many reports of studies confirming the existence of tetrahedral intermediates.[29] Prior to Bender's work[28] the possibility of nucleophilic attack concerted with leaving group departure was summarized by Dewar,[30] who stated that the nucleophile attacked the trigonal carbon in line with the leaving atom. If concerted attack were to occur, the out of line stereochemistry is probably favored since an acceptor p orbital on the trigonal carbon would be of lower energy than the orbital antibonding to the σ bond between trigonal carbon and leaving atom.[31] Consideration of the potential energy diagram (Figure 9) for the attack of nucleophile on an ester to yield the trigonal product indicates that a concerted process is likely if the tetrahedral intermediate has an energy which is high enough to inhibit the usual stepwise addition–elimination pathway. In some esters the increase in energy of this latter intermediate by steric constraint forces the hydrolysis mechanism to an elimination–addition extreme where an acyl cation is involved (path through the top left corner of Figure 9).[32] The elimination–addition path[33] can also be favored by stabilizing the acyl cation with an electron-donating substituent such as an *N,N*-dialkyl group; in this case the acyl chloride would yield a tetrahedral intermediate which may not have a discrete existence due to the destabilizing influence of the good leaving group and electron-donating substituent. It is quite possible, bearing in mind the above arguments, that a balance of effects could combine to favor a concerted process of acyl-group transfer.

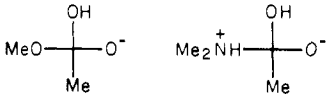
So far as the authors are aware there have been few serious reports of concerted acyl-group-transfer reactions in polar solution. Gaetjens and Morawetz[34] proposed that the considerable phenoxyanion character of the transition state in the cyclization of aryl glutarates and succinates was evidence for a concerted process. The β_{LG} value of unity for both succinates and glutarates may be coupled with the β value for the equilibrium between ester and phenoxide ion (1.7) to yield a transition-state index for cleavage of the ArO–C bond indicating extensive fission (eq 14). Unlike



the present case we are not able to place a figure on the extent of bond formation for the attacking nucleophile. An explanation of the high selectivity to leaving group in terms of a tetrahedral intermediate is that the breakdown of the latter is rate limiting; although we are not in a position to argue conclusively it is possible that the return of the intermediate (eq 15) to starting ester is retarded compared with fission to anhydride and phenolate because of entropy effects and because of the known stability of glutaric and succinic anhydrides.



Relatively accurate estimates have been made of the lifetimes of tetrahedral intermediates which might be expected in various acyl-group-transfer reactions.[21b,29c,35] A direct measurement of the decomposition of dimethyl hemiorthoformate in acetone–water at −35 °C has indicated that these estimates are at least of the correct order of magnitude.[36] The magnitude of these rate constants for anionic and zwitterionic tetrahedral intermediates (VII and VIII) is of the order 10^7–10^{10} s^{-1}; provision of more



VII VIII

powerful leaving groups such as chloride or activated phenolate anion could yield a tetrahedral adduct in a favorable case which cannot exist as a discrete compound ($t_{1/2}$ less than that of a bond vibration 10^{-13} s), thus favoring a concerted displacement; in this context there has recently been a challenge to the conventional postulate of a stepwise mechanism of acylation in chymotrypsin catalysis.[37]

Instability of the tetrahedral intermediate has been suggested to cause a change in mechanism to concerted in the hydrazinolysis of acylimidazoles.[38] The intermediate has a strong driving force

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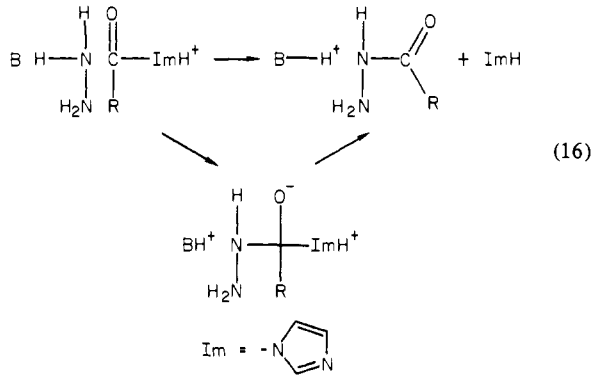
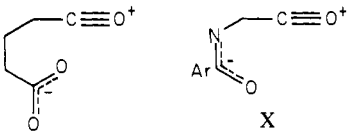
for breakdown provided by the electron pairs on the oxyanion and nitrogen atoms and the developing resonance of the amide product (eq 16).



(16)

The acylium ions from the intramolecular reactions of succinate and glutarate half esters and of aryl benzoylglycinates possess highly electron-donating moieties (IX and X, respectively) which



IX X

may act as stabilizing functions; the potential energy surface (Figure 9), usually highly asymmetric in favor of an addition-elimination mechanism, may therefore be rendered more symmetrical, shifting the reaction coordinate toward the top left corner favoring a concerted process. The free energy of the tetrahedral adduct in the intramolecular reaction will also be greater than that in the open chain because of a greater degree of internal rotational freedom in the latter; this also helps to promote a concerted displacement process.

Electron Spin Resonance Studies on Tris(3,5-di-*tert*-butylphenyl)silyl and -germyl Radicals[1]

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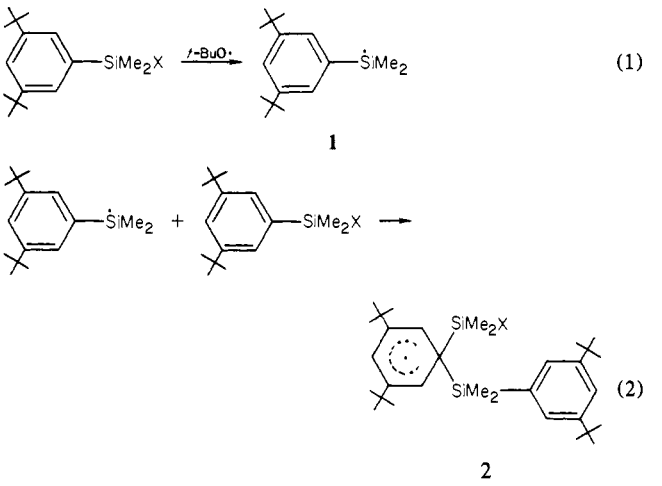
Abstract: Electron spin resonance spectra of tris(3,5-di-*tert*-butylphenyl)silyl, -germyl, and -methyl radicals in solution are recorded. The hyperfine coupling constants of the triarylsilyl radical are observed for the first time. The *g* values and hyperfine coupling constants, $A_{o\text{-}H}$ and $A_{p\text{-}H}$ (in gauss), are as follows: $Ar_3C\cdot$ (−40 °C), 2.0026, 2.58, 2.80; $Ar_3Si\cdot$ (−50 °C), 2.0027, 0.95, 1.17; $Ar_3Ge\cdot$ (−70 °C), 2.0056, 0.60, 0.95 (Ar = 3,5-di-*tert*-butylphenyl). The spin densities at the central atoms of $Ar_3M\cdot$ are estimated to be 0.50 (M=C), 0.78 (M = Si), and 0.82 (M = Ge), respectively.

Aryl-substituted radicals are of considerable interest to study by electron spin resonance (ESR) techniques, since ESR data give direct information about spin delocalization onto the aryl rings. Particularly interesting would be the ESR spectra of aryl-substituted group 4B radicals which could be compared with those of well-documented triarylmethyl radicals. These data could give useful information about the efficiency of spin delocalization from the central group 4B atom to 2p orbitals and may be related to the efficiency of C=M (M = Si, Ge, etc.) bonding which has been of current interest.

We have previously reported the ESR spectra of phenyl-substituted germyl radicals,[2] but, in spite of repeated experiments, we could not observe a neat spectrum of $Ph_3Si\cdot$ radicals. A reason that we failed to observe $Ph_3Si\cdot$ seemed to be the high reactivity of silyl radicals toward aromatic substitution.[3] The reaction of (3,5-di-*tert*-butylphenyl)dimethylsilane with the *tert*-butoxy radical gave a strong ESR signal of the ipso substituted radical (**2**) instead of the expected (3,5-di-*tert*-butylphenyl)dimethylsilyl radical (**1**).[4]

However, hydrogen abstraction from tris(3,5-di-*tert*-butylphenyl)silane gave the desired tris(3,5-di-*tert*-butylphenyl)silyl radical (**3**) successfully. In this paper, we report ESR studies on **3** and related methyl and germyl radicals.



(1)

1

(2)

2

X = H, D

Results and Discussion

The tris(3,5-di-*tert*-butylphenyl)silyl radical (**3**) was generated in an ESR cavity by abstraction of hydrogen from the corresponding hydrosilane using photochemically generated *tert*-butoxy radicals.[5,6]

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