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THE N-ETHYLBENZISOXAZOLIUM CATION—II

THE MECHANISM OF REACTIONS OF THE CATION WITH NUCLEOPHILES

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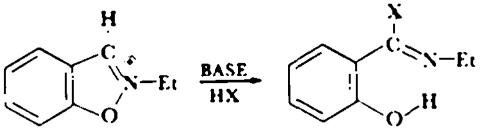
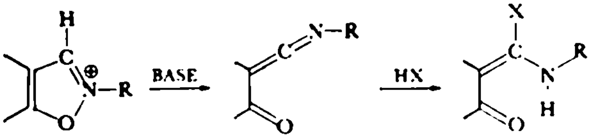
Abstract—The N-ethylbenzisoxazolium cation has been shown to undergo a ready general base-catalyzed internal elimination to form a transitory N-ethylbenzoketoketenimine. Alternative pathways involving benzoisoxazolines have been excluded by kinetic evidence and by study of the model substance, 2-ethylbenzo-4-isoxazoline. A competition study has shown that the intermediate benzoketoketenimine exhibits high selectivity in many of its combination reactions, and that for aqueous acetic acid in the pH range of 2–5 the reactive nucleophiles are most probably water and acetate ion.

INTRODUCTION

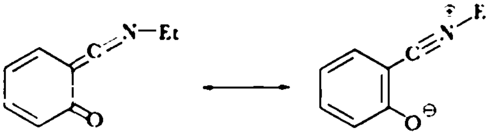
AS DESCRIBED in the first paper of this series,[2] the N-ethylbenzisoxazolium cation (I) shares with simple isoxazolium salts a high lability toward bases, and the capacity for combining in basic media with nucleophiles to form imido derivatives of general structure II. For reactions of isoxazolium salts, the problem of mechanism has been resolved by Woodward and Olofson, who observed that ketoketenimines are intermediates which may be detected directly under proper conditions.[3] As noted previously,[2] the mechanism of the reactions of I cannot be determined as easily, for under a wide variety of experimental conditions these reactions proceed without intervention of observable intermediates.



I II



While a very high reactivity might be expected for the benzoketoketenimine (III), which must partake either of zwitterionic or of *o*-xylylenic character, by the same



III

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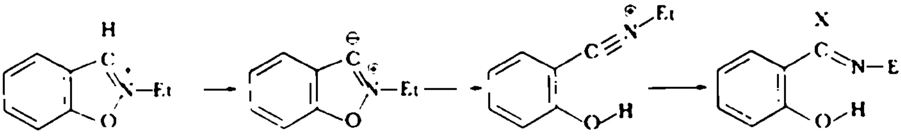
[2] D. S. Kemp and R. B. Woodward, *Tetrahedron* **21**, 3019 (1965).

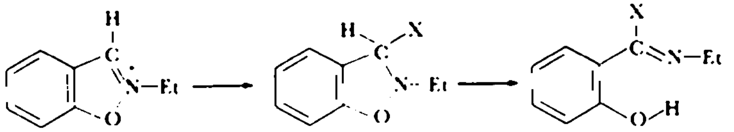
[3] R. B. Woodward and R. A. Olofson, *J. Am. Chem. Soc.* **83**, 1007 (1961).

token, III might be expected to be less stable, relative to its precursors, than simple ketoketenimines, and the question arises whether reactions of I could proceed by pathways which differ radically from those followed by the monocyclic isoxazolium salts. In addition to examining these issues, a mechanistic study of the reactions of I offered a chance to relate the chemistry of isoxazoles to that of other 5-ring heteroaromatic systems whose base-catalyzed exchanges and decompositions have been subject to much interest and attention in recent years.

The plausible mechanistic sequences for the decomposition of isoxazolium salts fall into two classes. For the members of one, *C—H* bond cleavage precedes *C—X* bond formation, and a ketoketenimine or its conjugate acid must intervene in the reaction sequence; for the other, mechanisms are initiated by *C—X* bond formation, and benzisoxazolines are obligatory intermediates. Provided that *C—H* cleavage occurs at the rate-determining step of the decomposition of I, these general mechanistic classes can be distinguished by a combined rate and product study, for mechanisms involving isoxazolines must show a correspondence between the rate attributable to a nucleophile and quantity of product derived from that nucleophile, while mechanisms involving benzoketoketenimines allow rates and products to vary independently.



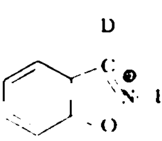
Class I: C—H cleavage precedes C—X formation



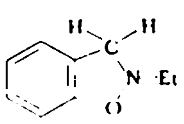
Class II: C—X formation initiates reaction

FIG. 1

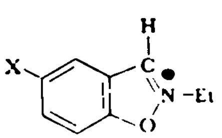
To decide this issue, rate and product studies of the reactions of I with aqueous carboxylic acid species were carried out. Further mechanistic information was available from the behavior of the deuterio compound (IV), the model benzisoxazoline (V), and the substituted benzisoxazolium salts VI and VII,



IV



V



VI C -- NO_2
VII X = SO_2Cl

EXPERIMENTAL

IR spectra were measured with a Perkin-Elmer Infracord Model 137 spectrometer and calibrated with the 6·24 μ band of polystyrene, NMR spectra were taken on a Varian Associates Model A-60 spectrometer, and UV spectra were taken on a Cary Model 14 spectrometer. Corrected m.ps were taken in pyrex capillary tubes, using a calibrated set of thermometers. Elemental analyses were performed by Scandinavian Microanalytical Laboratories of Copenhagen.

3-*Deuterio-2-ethylbenzisoxazolium fluoborate* (IV). Deuteriobenzisoxazole was prepared from 2-deuterioformyl phenol[4] by pyrolysis of the oxime acetate as described.[5] 9·0 g oxime acetate yielded 1·5 g, 25% of 3-deuteriobenzisoxazole, b.p. 35–40° at 2 mm. Alkylation of 1·0 g 3-deuteriobenzisoxazole with 2·0 g recrystallized triethyloxonium fluoborate in 5 ml CH_2Cl_2 yielded 1·55 g crude product which was recrystallized twice from MeCN, powdered, dried, and stored in a dark container; m.p. 109·4–110·5°, mixture m.p. 109·4–110·5° with a specimen of protio salt. By NMR analysis the salt was shown to contain less than 3% protium in its 3-position.

Aqueous exchange of the 3-deuterio-2-ethylbenzisoxazolium cation. A soln of 0·44 g 3-deuterio-2-ethylbenzisoxazolium fluoborate in 0·4 ml MeCN was added to a pH 2·5 buffer prepared by dissolving 0·5 g of Na_2SO_4 in 5 ml water containing 2 drops of conc. H_2SO_4. After 80 min at 25° UV analysis indicated that 60% of the cation had decomposed; the reaction was terminated by the addition of 1·0 ml conc. $HClO_4$ and 1·5 g $NaClO_4$. The precipitated perchlorate salt was collected, washed with H_2O and CH_2Cl_2, and dried to yield 70 mg of a substance, identical in all respects with an authentic sample of 3-deuterio-2-ethylbenzisoxazolium perchlorate; m.p. of recovered salt, 119·0–120·0°; m.p. of reference sample, 121·0–122·0°; mixture m.p., 119·0–120·0°. By NMR analysis the recovered salt was shown to contain less than 2% of protium in its 3-position.

2-*Ethyl-2,3-dihydrobenzisoxazole* (V). A soln of 10·0 g (0·043 mole) N-ethylbenzisoxazolium fluoborate in 10 ml CH_3CN was added to a slurry of 100 ml water and 50 g ice containing 1 ml of 12N HCl. The slurry was stirred vigorously during the addition of 5·0 g (0·13 mole) $NaBH_4$ in 15 ml water. The resulting alkaline mixture was extracted with seven 10 ml portions of CH_2Cl_2. The organic layers were combined and extracted, first with two 20 ml portions of 3N NaOH, then with three 20 ml portions of 1N HCl. The acid extracts were brought to pH 13 by the addition of 5N NaOH, and the resulting emulsion was extracted with three 10 ml portions of CH_2Cl_2 which were pooled, dried over $MgSO_4$, and evaporated. The residue was distilled to yield 1·2 g of a pale yellow oil, 19%, b.p. 38·5–40·0° at 0·5 mm. The distillate was taken up in anhydrous ether and precipitated as a hydrochloride by the addition of ether containing dry HCl. The crude salt was subjected to repeated fractional precipitation from dichloromethane–ether to remove an insoluble yellow oily impurity and then was converted to the free base with NaOHaq. The resulting oil was distilled: b.p. 91·7–92·0° at 16 mm $\eta_D^{24°}$ = 1·5359. (Found: C, 72·25; H, 7·60; N, 9·49. $C_9H_{11}NO$ requires: C, 72·41; H, 7·43; N, 9·39%.)

UV[6] (H_2O, pH 5–12): 280 mμ (2,200); (H_2O, pH 1): rev 276 (1,620), 269 mμ (1,720). NMR (CCl_4): 2·9–3·5 τ (4 protons, m), 5·9 τ (2 protons, broad s), 7·2 τ (2 protons, q), 8·9 τ (3 protons, t).

Demonstration of the stability of 2-ethyl-2,3-dihydrobenzisoxazole to aqueous base. A homogeneous soln of 0·20 g purified 2-ethyl-2,3-dihydrobenzisoxazole in a mixture of 0·15 g NaOH, 3 ml MeOH, and 3 ml water was allowed to stand for 4 days at 25°, then was extracted with ten 1 ml portions of n-pentane. The extracts were combined, dried over Na_2SO_4, and evaporated through a 10 cm helix-packed column. Bulb-to-bulb distillation of the residue yielded 0·16 g, 80%, of oil whose IR spectrum was that of the dihydrobenzisoxazole, $\eta_D^{24°}$ = 1·5356.

5-*Nitro-2-ethylbenzisoxazolium fluoborate* (VI). By the procedure of Lindemann,[5] benzisoxazole was nitrated to yield 5-nitrobenzisoxazole, m.p. 126·5–127·5° after crystallization from MeCN, reported m.p., 126°. To a solution of 12 g (0·061 mole) recrystallized triethyloxonium fluoborate in 15 ml CH_2Cl_2 was added 10·0 g (0·061 mole) 5-nitrobenzisoxazole. After 48 hr at 25° the solution had deposited 16·9 g, 98%, of crude salt, m.p. 134·8–137·0°. Four recrystallizations from MeCN–AcOEt raised the m.p. to 136·2–138·0°. (Found: C, 38·61; H, 3·55; N, 9·97. $C_9H_9N_2O_3BF_4$ requires: C, 38·61; H, 3·24; N, 10·01%.) NMR(MeCN): 0·0 τ (1 proton, s), 0·9–2·0 τ (3 protons, m), 5·1 τ (2 protons, qu).

*Hydrolysis of 5-nitro-2-ethylbenzisoxazolium fluoborate to 5-nitro-*N*-ethylsalicylamide.* A soln of 1·0 g (3·6 mmole) 5-nitro-2-ethylbenzisoxazolium fluoborate in 2 ml MeCN was added to 15 ml 10% $HClO_4$, whereupon a ppt formed within a few sec. After 5 min the amide was collected and recrystallized from EtOH–water to yield 1·2 g, 80%, m.p. 162·0–163·8°. Recrystallization and sublimation

[4] Prepared by a Reimer-Tiemann reaction conducted in D_2O; unpublished work of D. S. Kemp and R. B. Woodward.

[5] H. Lindemann and H. Thiele, *Liebigs Ann.* **449**, 63 (1926).

[6] Compare with λ_{max}^{EtOH} 277 mμ (1,725) 271 mμ (1,725) reported[7] for *o*-methoxytoluene.

[7] A. Burawoy and J. T. Chamberlain, *J. Chem. Soc.* 2312 (1952).

raised the m.p. to 163·4–163·8°. (Found: C, 51·61; H, 4·96; N, 13·25. $C_9H_{10}N_2O_4$ requires: C, 51·43; H, 4·80; N, 13·33%.)

5-Chlorosulfonylbenzisoxazole. Benzisoxazole, 30 g (0·27 mole), was added slowly to 250 g of cooled, freshly distilled $ClSO_3H$. The resulting soln was heated with stirring for 27 hr on the steam bath, then was chilled, combined with 500 ml of CH_2Cl_2, and poured cautiously onto 3 kg of crushed ice. When the ice had completely melted, the layers were separated, and the aqueous layer was extracted with two 100 ml portions of CH_2Cl_2. The pooled CH_2Cl_2 extracts were washed with 100 ml water, dried over $MgSO_4$, and evaporated to yield 37 g, 67%, of an oil which quickly solidified, m.p. 69·0–70·5°. Recrystallizations and sublimations raised the m.p. to 70·3–71·0°. (Found: C, 38·76; H, 2·18; N, 6·42; S, 14·49; Cl, 16·11. $C_7H_{14}ClNO_3S$ requires: C, 38·62; H, 1·85; N, 6·44; S, 14·73; Cl, 16·29%.)

2-*Ethyl-5-chlorosulfonylbenzisoxazolium fluoborate* (VII). Recrystallized 5-chlorosulfonylbenzisoxazole, 10·0 g (0·46 mole), was dissolved in 15 ml CH_2Cl_2 containing 8·7 g (0·046 mole) recrystallized triethyloxonium fluoborate. After 48 hr at 25° the soln had deposited 14·5 g, 94%, of crude salt, m.p. 156·0–159·5°. Four recrystallizations from M–CN–benzene raised the m.p. to 157·6–159·0°. (Found: C, 32·44; H, 3·24; N, 4·34; Cl, 10·81. $C_9H_9NO_3SClBF_4$ requires: C, 32·41; H, 2·72; N, 4·20; Cl, 10·63%.) NMR(MeCN): −0·1 τ (1 proton, s), 0·9–1·9 τ (3 protons, m), 5·0 τ (2 protons, qu).

When a soln of the salt in MeCN was added to 10% $HClO_4$, a ppt formed almost immediately. After 5 min the amide was isolated by extraction with 10 ml CH_2Cl_2. The organic phase was separated, dried over $MgSO_4$, and evaporated. Crystallization of the resulting oil from $CHCl_3$ yielded 64% of a white solid, m.p. 156·0–158·5°, identifiable from its spectroscopic properties as 5-chlorosulfonyl-N-ethylsalicylamide. Two sublimations raised the m.p. to 158·7–159·7°. (Found: C, 41·05; H, 3·94; Cl, 13·64. $C_9H_{10}NO_4SCl$ requires: C, 40·99; H, 3·82; Cl, 13·45%.)

Other reagents and materials. AcOH (Mallinckrodt reagent grade), NaCl (Mallinckrodt reagent grade), and MeCN (Eastman spectrograde) were used without purification. Methoxyacetic acid (Eastman white label) was subjected to two distillations at 18 mm through a 40 cm spinning band column. With each distillation, the first quarter of the distillate was discarded, and the following two thirds of the sample was collected, b.p. 101° at 18 mm, $\eta_D^{24\cdot0} = 1\cdot4152$. N-ethylbenzisoxazolium fluoborate was recrystallized twice from MeCN, ground to a powder, dried overnight at 50° *in vacuo*, and stored in a foil-wrapped vial over P_2O_5, m.p. 109·5–110·2°.

Standard NaOH solns were prepared by diluting carbonate-free salt NaOHaq with boiled, distilled water, and were standardized against oven-dried potassium hydrogen phthalate. Solutions of carboxylic acids were prepared using boiled, distilled water which had cooled under N, and were standardized against NaOHaq using phenolphthalein as indicator. All volumetric glassware used in the kinetics experiments was cleaned between runs with chromic acid soln and seasoned for 4–5 hr in dil AcOH. *Equipment.* A Radiometer *Model* 4 pH meter equipped with glass and calomel electrodes was used throughout the study. The electrodes were standardized before and after a series of measurements with a commerical phthalate buffer (pH 4·01). Measurements of pH were made at room temp, without thermostatic control.

Optical densities were measured using a Beckman *DU* Spectrophotometer equipped with a cell compartment thermostatted at 30·15 ± 0·03°. Kinetic runs were for the most part carried out in 1·00 cm rectangular silica cells; for runs at high substrate concentrations the cell length was shortened to 0·200 cm by the introduction of a spacer.

Kinetic procedure. Rates of decomposition of I were measured at 30·15° in acetate and methoxyacetate buffers brought to an ionic strength of 0·10 with NaCl. With these buffers the reaction products are N-ethylsalicylamide and an O-acyl-N-ethylsalicylamide.[8] At 30° after 12 hr at pH 5, O-acetyl-N-ethylsalicylamide is hydrolyzed to the extent of 5%, and O-methoxyacetyl-N-ethylsalicylamide to the extent of 20%; since half-lives for reactions studied did not exceed 15 min, product hydrolysis did not complicate the study. Rates were followed at 258 mμ, an absorption maximum for I ($\epsilon = 13{,}100$). Although I was found to obey Beer's law over the concentration range of the study, and the O-acylsalicylamides show flat, low intensity absorption at 258 mμ, the absorption spectrum of N-ethylsalicylamide in this region is characterized by a steep slope with an extinction of 2000 at 258 mμ. Despite this slope, the overall deviations from Beer's law are not significant, for ester is the major product at all but the smallest buffer strengths.

Reaction mixtures contained 1% of MeCN, but this substance may be eliminated as a catalytic species since runs at pH 1 in its presence and absence gave identical rates.

Mean buffer ion concentrations were calculated from Eq. 1. Mean acidities were calculated from the observed

$$[RCO_2]_m = [Na^+] + [H^+]_m - [Cl^-] - \frac{[BF_4]}{2} \qquad (1)$$

initial and final pH's. The pH measurements conducted at 22–25° could be assumed to apply without correction to the solutions at 30·15° since the coefficient of thermal variation of ionization constant for carboxylic acids is small.[8] The hydroxide ion concentrations were calculated by dividing Harned's value[9] of $2{\cdot}43 \times 10^{-14}$ for the ion product of water at 30° in the presence of 0·1N NaCl by the antilogarithm of the mean value of the pH observed at 22–25.°

For the kinetic measurements appropriate volumes of a stock buffer solution prepared from standard NaOH and carboxylic acid solns were combined with water and NaCl in a 100 ml volumetric flask. The pH of this soln was brought to the value desired for the series by the addition of a trace of stock carboxylic acid, and the flask was equilibrated at 30·1°. To begin a run, 1·00 ml of a standard solution of N-ethylbenzisoxazolium fluoborate in MeCN was added to a flask, the contents were mixed and brought to the mark, and a portion was transferred to a silica cell. Optical density measurements were made until the reaction was at least 90% complete. Values for the initial optical density were estimated from the known absorptances of I and of the buffer soln; values for the optical density at infinite time were approximated by a measurement after ten half-lives—these values corresponded satisfactorily with values calculated from the known product composition. All measurements followed first-order kinetics; pseudo-first order rate constants were determined graphically, and constants obtained at fixed pH were fitted to an equation linear in buffer anion concentration by a least squares procedure, which was also used to obtain approximate estimates of the standard deviations of slopes and intercepts. The zero intercepts from these fittings were plotted against hydroxide concentration, and the slope of this plot was estimated graphically. The results of the kinetic measurements are summarized in Table 1, and an analysis is presented in Table 2.

Analysis and procedure used in the product study. Careful analysis by direct isolation and by IR and UV spectrophotometry revealed that N-ethylsalicylamide and O-acetyl-N-ethylsalicylamide comprise at least 98% of the products formed by reaction of I with aqueous AcOH solns in the pH range 2–6. The product assay was further simplified by the observation that at the long wavelength absorption max of N-ethylsalicylamide (297 mμ, ϵ = 3,580), O-acetyl-N-ethylsalicylamide shows no absorption. Thus in principle a single measurement could be used to assay the composition of the product mixture. However, since the initial amount of I used in these reactions was not known with the accuracy of the photometric measurements, a further measurement was carried out in which all salicylamide species were converted at pH 11 to the N-ethylsalicylamide anion (λ_{max}, 325 mμ, ϵ = 6,070).

Since the substrate concentrations employed in this study were of necessity higher than those used in the kinetic measurements, a marked pH drift was anticipated at low acetate concentrations. This problem was handled by allowing a controlled drift through a mean pH value which was constant for a series of determinations. For each run at fixed pH, an approximate initial acidity was calculated from Eq. (2) where subscript *m* terms refer to mean values, and the soln was adjusted to this value by

$$[H^+]_i \doteq \frac{[OAc^-]m[H^+]m - Ka[BF_4^-]/2}{[OAc^-]m + [BF_4^-]/2} \qquad (2)$$

the addition of dil AcOH. The acidity was redetermined after the completion of the reaction, and the mean of the initial and final values was taken. The mean acetate concentration was calculated from Eq. (1).

For the measurements themselves, NaCl sufficient to bring the ionic strength to 0·10 was added to acetate buffer and water contained in a 100 ml volumetric flask, the solution pH was adjusted with AcOH as described above, and the mixture was brought to 30·1°. Exactly 1·00 ml of a standard solution of N-ethylbenzisoxazolium fluoborate in acetonitrile was added, the solution was brought to the mark with water, mixed, and the flask returned to the constant temp bath for 10 half-lives. The optical density at 297 mμ was then measured and a 25·0 ml aliquot of the soln was brought

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[8] R. G. Bates, *Determination of* pH, p. 115. Wiley New York, (1964).

[9] H. S. Harned, *The Physical Chemistry of Electrolyte Solutions*, p. 638. Rheinhold, New York (1958); H. S. Harned and G. E. Marmweiler, *J. Am. Chem. Soc.* 57, 1873 (1935).

TABLE 1. RATES OF DECOMPOSITION OF THE N-ETHYLBENZISOXAZOLIUM CATION

T = 30·15° μ = 0·10 Aqueous solutions 1% in acetonitrile

A. *Acetate buffers*

$pH_{average}$	pH_{drift}	Acetate[a] concentration	Rate constant (Minutes^{-1})	$\sigma \times 10^{3}$[b]
3·81	+0·010	0·0151	0·302	10
3·82	−0·016	0·0101	0·270	3
3·82	+0·010	0·0051	0·266	5
3·82	+0·000	0·0021	0·253	5
3·65	+0·010	0·0152	0·221	4
3·65	+0·002	0·0102	0·192	3
3·65	−0·011	0·0052	0·182	6
3·65	−0·007	0·0022	0·177	4
3·43	+0·006	0·0153	0·156	4
3·43	+0·001	0·0103	0·144	3
3·43	−0·001	0·0053	0·126	6
3·41	−0·013	0·0023	0·112	5
3·41	−0·006	0·0013	0·107	5
3·34	+0·013	0·0154	0·149	6
3·33	−0·005	0·0104	0·129	6
3·33	−0·009	0·0054	0·109	6
3·33	−0·010	0·0024	0·0935	7
3·33	−0·014	0·0014	0·0923	6
2·94	−0·007	0·0161	0·107	6
2·94	+0·004	0·0111	0·0871	5
2·94	−0·007	0·0061	0·0635	5
2·94	−0·011	0·0031	0·0484	4
2·94	−0·015	0·0021	0·0427	5
3·43[c]	−0·009	0·0153	0·0722	3
3·43	+0·004	0·0103	0·0574	3
3·43	−0·001	0·0053	0·0422	3
3·41	−0·015	0·0023	0·0335	4
3·41	−0·013	0·0013	0·0300	4

B. *Methoxyacetate buffers*

$pH_{average}$	pH_{drift}	Methoxyacetate[a] concentration	Rate constant (minutes^{-1})	$\sigma \cdot 10^{3}$[b]
3·45	−0·009	0·0153	0·120	5
3·45	+0·011	0·0103	0·110	3
3·44	+0·005	0·0053	0·113	3
3·44	−0·006	0·0023	0·109	3
3·27[d]	−0·001	0·0153	0·0767	4
3·27	−0·005	0·0103	0·0796	4
3·28	−0·028	0·0053	0·0780	6
3·26	+0·007	0·0105	0·0767	5
3·26	+0·004	0·0025	0·0720	5
3·26	+0·000	0·0015	0·0720	5
3·07	−0·030	0·0158	0·0519	4
3·07	+0·030	0·0108	0·0504	4
3·07	+0·020	0·0058	0·0488	6
3·06	−0·020	0·0028	0·0477	3
3·05	−0·020	0·0018	0·0456	4
2·86	−0·009	0·0164	0·0372	4
2·86	−0·003	0·0114	0·0355	6
2·86	−0·003	0·0034	0·0308	5
2·85	−0·003	0·0024	0·0312	6

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[a] Calculated from Eq. (1).

[b] $\sigma = \sqrt{\frac{\Sigma(xi - \bar{x}i)^2}{n - 1}}$; n is No. of observations, *xi* is $\log\left(\frac{ODo - OD\infty}{ODt - OD\infty}\right)$,
$\bar{x}_i = a_0 + kt/2{\cdot}3$.

[c] The final set of rates at pH 3·43 used the deuterio derivative (IV) as substrate. To minimize experimental variations these runs were interlaced with the corresponding measurements at pH 3·43 conducted with I, and stock solutions and pH determinations were prepared and executed under nearly identical conditions.

[d] For the first three rate measurements at pH 3·27, the substrate concentration was $3{\cdot}8 \times 10^{-4}$N; for the second three, $0{\cdot}38 \times 10^{-4}$ N.

TABLE 2. ANALYSIS OF RATE DATA

pH	Hydroxide[a] concentration	Slope l/m-min	σ	Intercept min^{-1}	σ	Calculated[b] intercept
1. *Acetate buffers*						
3·82	16·1 . 10^{-11}N	3·4	±0·8	0·244	±0·008	0·260
3·65	10·9	3·3	0·9	0·167	0·007	0·175
3·43	6·40	3·5	0·3	0·105	0·002	0·103
3·32	5·19	4·2	0·1	0·0855	0·001	0·0838
2·97	2·11	4·6	0·2	0·0343	0·001	0·0341
3·43[c]	6·40	3·0	0·2	0·0263	0·0002	
2. *Methoxyacetate buffers*						
3·45	6·69 . 10^{-11}N	0·7	±0·4	0·107	±0·004	0·108
3·26	4·39	0·4	0·2	0·0729	0·002	0·0709
3·07	2·85	0·40	0·07	0·0459	0·0006	0·0460
2·86	1·72	0·47	0·04	0·0297	0·0004	0·0278

[a] $[OH^-] = (2{\cdot}430 \times 10^{-14})/[H^+]$.

[b] Calculated Intercept = $1{\cdot}62 . 10^9 [OH^-]$.

[c] Constants obtained using the deuterio cation IV as substrate.

to pH 11 with NaOH and diluted to 100·0 ml. The optical density of this soln was measured at 325 mμ and the product ratio was calculated from expression (3). A typical set of data is shown in Table 3, and the results

$$\frac{[\text{N-ethylsalicylamide}]}{[\text{O-acetyl-N-ethylsalicylamide}]} = \frac{OD_{307} . 6{\cdot}07}{4 . 3{\cdot}58 . OD_{335} - OD_{307} . 6{\cdot}07} \qquad (3)$$

of all measurements are summarized in Table 4.

Estimates of the nucleophilicities of azide, cyanate, and thiourea relative to acetate were obtained by adding I to solns containing known amounts of acetate and the second nucleophile at pH 5, and monitoring the resulting solution after 15 min at an absorption max of product derived from azide, cyanate, or thiourea.

TABLE 3. ACETATE PRODUCT STUDY AT pH 4·26

	T = 30·15°				μ = 0·10	
pH_i	pH_f	$\frac{1}{[OAc^-]}$	OD_{307}^a	OD_{335}	$\frac{\text{phenol}}{\text{acetate}}$	Calculated ratio
4·264	4·263	17·8	0·089	0·685	0·057	0·061
4·265	4·257	35·6	0·152	0·675	0·105	0·106
4·274	4·262	59·5	0·225	0·672	0·165	0·166
4·264	4·252	90·1	0·302	0·639	0·251	0·243
4·277	4·267	100	0·336	0·672	0·268	0·268
4·262	4·250	120	0·385	0·674	0·320	0·319
4·278	4·251	151	0·450	0·670	0·398	0·397
4·282	4·248	182	0·510	0·671	0·478	0·475
4·275	4·216	263	0·642	0·671	0·682	0·679
4·282	4·203	373	0·767	0·666	0·954	0·957

[a] 10·4 mg of I was added to each flask.

[b] Calculated ratio = $\left(\frac{2{\cdot}52}{[OAc^-]} + 16{\cdot}5\right) 10^{-3}$.

TABLE 4. SUMMARY OF WATER-ACETATE COMPETITION EXPERIMENTS

		T = 30·1°	μ = 0·10	
pH	Number of observations	Acetate ion concentration range	10^3 . Zero intercept*	10^4 × Slope*
4·26	10	0·06–0·003	16·5 ± 2	2·52 ± 0·01
3·93	10	0·06–0·003	9 ± 2	2·39 ± 0·01
3·71	9	0·04–0·002	13 ± 2	2·59 ± 0·01
3·55	9	0·03–0·002	5 ± 5	2·38 ± 0·01
3·33	10	0·02–0·0025	- 2 ± 12	2·36 ± 0·05
3·14	10	0·01–0·003	9·5 ± 5	2·33 ± 0·03
2·85	10	0·01–0·0035	18 ± 12	2·34 ± 0·05

* By a least squares procedure data were fitted to an equation linear in $\frac{1}{[OAc^-]}$, and estimates were obtained for standard deviations of slopes and intercepts.

RESULTS

The kinetic data summarized in Table 2 establish that the overall rate of decomposition of the N-ethylbenzisoxazolium cation in aqueous acetate and methoxyacetate buffers is linear in both hydroxide and carboxylate concentrations over the pH range of 2·5–4·5.[10] Values for catalytic constants are shown in Table 5; although the constants for hydroxide and acetate are determined accurately, the corresponding value for methoxyacetate is less well defined since the maximum contribution of methoxyacetate to an observed rate was only 20%. In a more extreme form the same difficulty arose with attempts to detect catalysis by water. At 30° in 0·1N HCl the N-ethylbenzisoxazolium cation decomposes with a first-order rate constant of 1·3 × 10^{-5} sec^{-1}. Since the calculated rate for hydroxide catalysis at pH 1 in 0·1N NaCl is 6·3 × 10^{-6} sec^{-1}, and the extrapolation from 0·1N NaCl to 0·1N HCl may be expected to create uncertainties in rate of at least 20–30%, the value quoted in Table 5 for the water constant is accurate at best to half an order of magnitude.

TABLE 5. CATALYTIC CONSTANTS FOR THE DECOMPOSITION OF I

T = 30·1° Species	μ = 0·10 Catalytic constant
Hydroxide	2·7 × 10^7 liters $mole^{-1}$ sec^{-1}
Acetate	7·0 × 10^{-3}
Methoxyacetate	7 × 10^{-3}
Water	1 × 10^{-7}*

* Calculated assuming a_{H_2O} = 55.

The primary kinetic isotope effect reported in Table 6 for reaction of the benzisoxazolium cations I and IV with hydroxide requires that in the rate-determining step of the decomposition, proton abstraction must occur. The observation that the decomposition of the deuterio derivative IV follows simple first-order kinetics strongly implies that in addition to being rate-determining, *C—H* cleavage is also irreversible. A more sensitive demonstration of this point was provided when pure IV was allowed

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[10] The slight increase observed in the acetate catalytic constant as the pH is lowered is almost certainly a medium effect. At pH 2·94 with an acetate concentration of 0·015, the soln is 6% by weight in acetic acid, and would be expected to show a small increase in activity coefficients for charged species.

TABLE 6. KINETIC ISOTOPE EFFECT IN ACETATE BUFFERS

T = 30·1°	$\mu = 0{\cdot}1$	pH = 3·32
Hydroxide: kH/kD	$= \frac{0{\cdot}105 \pm 0{\cdot}002}{0{\cdot}026_3 \pm 0{\cdot}0002}$	$= 4{\cdot}0 \pm 0{\cdot}1$
Acetate: kH/kD	$= \frac{4{\cdot}2 \pm 0{\cdot}1}{3{\cdot}0 \pm 0{\cdot}2}$	$= 1{\cdot}4 \pm 0{\cdot}2$

to decompose in an aqueous bisulfate buffer; after 60% decomposition had occurred, fully deuterated IV was recovered from the medium.

A general scheme which describes the formation of O-acetyl-N-ethylsalicylamide and N-ethylsalicylamide from I, based on the general principles set forth in paper I of this series, is given in Fig. 2. The unusual feature which this scheme presents is the two-fold path of decomposition open to the highly activated intermediate X. From this scheme, expression (5) may be derived, relating the product ratio VIII:IX to acidity and acetate ion concentration. The slope term, F([H⁺]), is a function of acidity alone, and corresponds to

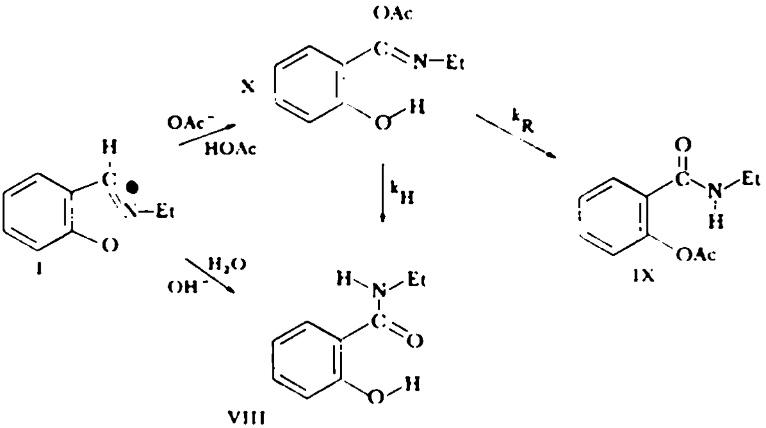

FIG. 2

$$\frac{\text{VIII}}{\text{IX}} = \frac{\text{phenol}}{\text{ester}} = \frac{1}{[\text{OAc}^-]} \cdot F([\text{H}^+]) \cdot \left(1 + \frac{kH}{kR}\right) + \frac{kH}{kR} \tag{5}$$

the product ratio which would be observed at unit acetate ion concentration, fixed acidity, and in the absence of hydrolysis of X. The intercept term, kH/kR, represents the product ratio which would be observed in the hypothetical situation of unit water activity and infinite acetate concentration; it therefore sets a bound on the realizable yield of ester IX which can be obtained from reaction of I with acetate species in water.

From the data of Table 4 it is clear that the slope term remains constant over the pH range of the study, and that the intercepts are not significantly different from zero[11] (for example, with $kH/kR = 16 \times 10^{-3}$, at infinite acetate ion concentration, the product would consist of 1·6% VIII and 98·4% IX). As a result the product study

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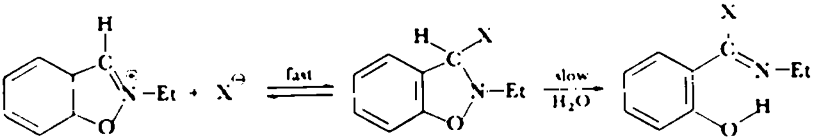
[11] Strictly speaking, this demonstration is invalid if kH/kR is proportional to 1/[OAc⁻]. While one can conceive of general base catalyzed rearrangement processes with β such that acetate catalysis predominates over the concentration range of the study, they seem rather improbable, and fail to affect the practical consequences of the observation of a zero intercept term.

demonstrates that expression (6) describes the product ratio observed for reaction of I with acetate buffers over the pH range of 2·5–4·5.

$$\frac{\mathrm{VIII}}{\mathrm{IX}} = \frac{2{\cdot}4\,.\,10^{-3}}{[\mathrm{OAc}^-]} \tag{6}$$

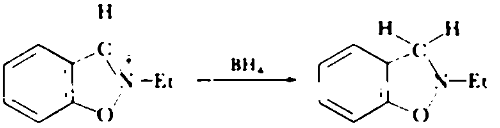
DISCUSSION

For a mechanism invoking the intermediacy of benzisoxazolines, the observation that the rate of decomposition of I is linear in carboxylate and hydroxide concentration and that *C—H* cleavage occurs in the rate determining step can be rationalized only if a benzisoxazoline is formed in a rapid equilibrium step, and subsequently undergoes a slow decomposition by reaction with water or its kinetic equivalent. The observed basic catalysis would then be nucleophilic catalysis, and the product ratio would be required to vary with the contribution of a nucleophile to the observed rate.



The results presented in the previous section prove that over the pH range of 2·5–4·5, the product ratio observed for the reaction of the N-ethylbenzisoxazolium cation with acetate and water species is independent of the contribution of acetate catalysis to the overall decomposition rate: for example, at an acetate concentration of 0·015M, the product composition remains constant at 87% of O-acetyl-N-ethylsalicylamide over the pH range of 2·97–3·82, while the contribution of acetate catalysis varies from 70% to 20% over this range of acidities. On this basis the kinetic results exclude benzisoxazolines as relevant intermediates in the decomposition of I.

This conclusion may be reached independently from the behavior of the model benzisoxazoline, V, obtained by the controlled reaction of I with sodium borohydride. This substance is stable to aqueous acids and bases, and can be recovered in a yield of 80% after 4 days in a homogeneous water-methanol mixture containing sodium hydroxide. From this result it is clear that benzisoxazolines are too inert to serve as intermediates in the cleavage reactions of benzisoxazolium salts.[12]



I V

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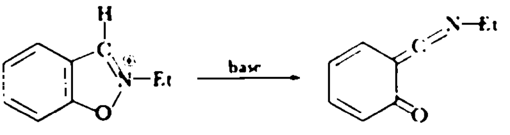
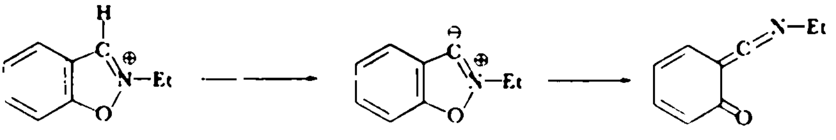
[12] A bound can easily be set on the magnitude of the discrepancy between the reactivity observed for V and that required for the benzisoxazoline mechanism. The rate constant for reaction of I with acetate is 4 l/m-min. Under the assumption that benzisoxazolines are intermediates, the observed second-order rate constant must equal kw/Kx, where kw is the rate constant for reaction of water with 3-acetoxy-2-ethylbenzisoxazoline, and Kx is the equilibrium constant for the formation of this species from I and acetate ion. Since the UV spectrum of I shows no diminution in solutions containing acetate, Kx must be greater than unity, whereupon kw must be greater than 4 min^{-1}. The recovery experiment cited in the text demonstrates that the first order rate constant for the reaction of V with water cannot exceed 5×10^{-6} min^{-1}. One can conclude, therefore, that as a lower bound, an acetoxybenzisoxazoline would have to be at least 10^6 times more reactive than V to contribute significantly to the decomposition of I.

Since one can now exclude mechanisms in which C—X formation precedes rate-determining C—H cleavage, one is left with a choice of mechanisms in which C—H cleavage initiates the mechanistic sequence, and which postulate a benzoketoketenimine or its conjugate acid as the true electrophilic species. A point which this evidence leaves unclear is the stage at which O—N bond cleavage occurs—although this process might readily be envisaged as occurring in concert with C—H cleavage, forming the benzoketoketenimine by a base-catalyzed *trans* elimination, it might equally be imagined as occurring in stages by way of an ylide species of a sort known to possess appreciable stability.[13] The observed failure of IV to incorporate protium during decomposition implies that XI, if present, must undergo rearrangement at least twenty times faster than reprotonation.



I III



I XI III

Evidence in support of a concerted cleavage reaction is available from the qualitative behavior of the substituted benzisoxazolium salts, VI and VII. These substances are converted to the corresponding salicylamides with half-lives of around a minute in 10% aqueous perchloric acid at 25°, and therefore can be estimated to be at least 10^4 times as reactive as I, a rate difference which is most easily rationalized as representing resonance stabilization of partial negative charge developed on oxygen at the transition state of a concerted *trans* elimination.[14]

A striking feature of the decomposition of I is the extreme rapidity of its catalysis by hydroxide ion, which lies only three orders of magnitude below that expected for a diffusion-controlled process.[15] The rate constant is approximately 10^8 times faster

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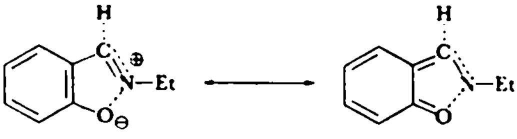
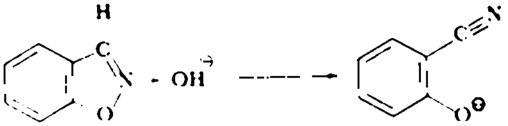
[13] R. Breslow, *J. Am. Chem. Soc.* **80**, 3719 (1958); R. A. Olofson, W. R. Thompson, and J. S. Michelman, *Ibid.* **86**, 1865 (1964).

[14] It could be argued that while the strongly activated 5-nitro and 5-chlorosulfonyl benzisoxazolium cations cleave by a concerted process, the less activated parent system may well react by a stepwise mechanism. This possibility seems unlikely, for while changes in mechanism are frequently observed as the result of changes in aromatic substitution, they occur with a change in the *character* of substitution, i.e. when electron-donating are replaced by electron-withdrawing substituents; for the case at hand, the *C—N* moiety constitutes a common electron-withdrawing function for I, VI and VII.

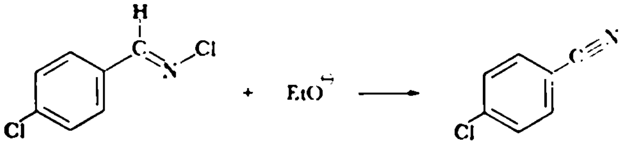


[15] M. Eigen, *Angew. Chem.* **75**, 489 (1963).

than that of the related hydroxide-catalyzed cleavage of benzisoxazole itself, which

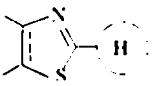


k = 1·5 . 10^{-1} l/m-sec H$_2$O, 25° [16]

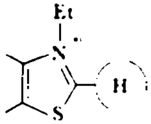


k = 1·8 l/m-sec EtOH, 30° [17]

lies in the range observed for related systems. Although the large rate increase observed for the introduction of a quarternary ethyl function can be attributed to the influence of both inductive and resonance effects, it is interesting that Olofson has observed a still larger rate effect for the hydroxide-catalyzed exchange reactions of thiazole and the 3-ethylthiazolium cation which appears to be largely inductive in origin.[18]



k = 5·8 . 10^{-8} l/m-sec
NaOD in D$_2$O, 31° [18]



k = 9·8 . 10^{8} l/m-sec
D$_2$O, 31° [18]

The selectivity which is the second remarkable feature of the base-catalyzed decomposition of I is more difficult to understand. The data of Table 5 must be regarded as an example of general base catalysis, and it is clear that the decomposition of I is rapid only when catalyzed by strong bases.[19] This result implies that despite the rapidity of the hydroxide-catalyzed decomposition, the transition states for reaction of I with bases must more closely resemble products than starting materials. While the sensitivity of transition state energy to strength of the component base

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[16] D. S. Kemp and M. T. Link, unpublished observations.

[17] W. E. Jordan, H. E. Dyas and D. G. Hill, *J. Am. Chem. Soc.* 63, 2383 (1941).

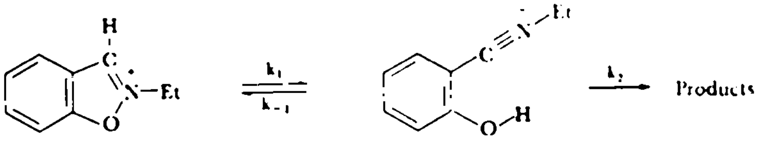
[18] R. A. Olofson, J. M. Landesberg and K. N. Houk, *J. Am. Chem. Soc.* 88, 4265 (1966). The author is grateful to Professor Olofson for communicating these results prior to publication.

[19] The results of a Bronsted analysis, although of tentative significance given the sparsity of data, are nonetheless interesting. The following values were calculated for $\beta = 0{\cdot}81$ and $G_B = 10^{4\cdot 9}$ l/m-sec.

Base	K_A	kcalc kcalc $= G_B \left(\frac{1}{K_A}\right)^{\beta}$	kobs
Hydroxide	$4{\cdot}4 \times 10^{-16}$	3×10^{7} l/m-sec	$2{\cdot}7 \times 10^{7}$ l/m-sec
Acetate	$2{\cdot}6 \times 10^{-5}$	7×10^{-2}	6×10^{-2}
Methoxyacetate	$4{\cdot}4 \times 10^{-4}$	7×10^{-3}	6×10^{-3}
Water	55	5×10^{-7}	1×10^{-7}

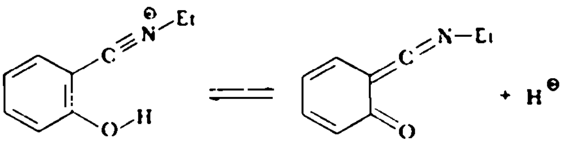
provides the most dramatic demonstration of this point, one also can regard the strong rate enhancement brought about by electron-withdrawing ring substituents, and the marked variation of kinetic isotope effect with base strength as manifestations of the same effect.

A possible explanation for product-like character of these transition states is that the benzisoxazolium salt is in fact slightly more stable than the isomeric benzoketo-keteniminium cation. Unfortunately, while accounting for their selectivity, this proposal fails to explain the rapidity of decompositions of I, for it requires that the energy barrier between two dissimilar species be low, and it seems unlikely that a process requiring rupture of two single bonds and much reorganization of electronic structure could occur readily without the incentive of a substantial energy gain.[20]

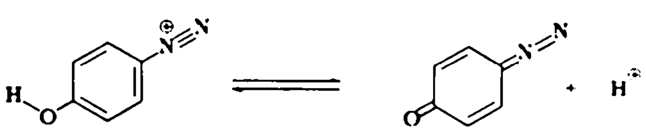


$k_2 > k_{-1} > k_1$

The evidence which has been advanced still leaves open the question of whether the benzoketoketenimine (III) or its conjugate acid (XII) is the reactive electrophile generated by the decomposition of I. Neither kinetic nor product studies can be used to decide this issue, although an interesting analogy is provided by the observation of Lewis and Johnson that the pK_a of p-hydroxybenzenediazonium ion is 3·4.[22] Since the electron-withdrawing effect of the nitrilium function might be expected to lie between that of a nitrile and a diazonium group, the pK_a of XII should lie in the range of 3·5–7·0, and both III and X might be expected to be present in significant concentration over the pH range of the relative rate study.



XII III



Provided only one of the electrophiles, III and XII, contributes to product formation, the observation that the N-ethylsalicylamide O-acetyl-N-ethylsalicylamide ratio is solely a function of acetate ion concentration establishes water and acetate

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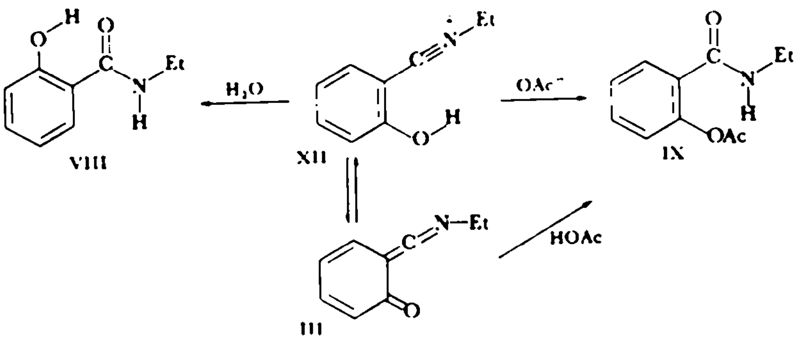
[20] The question of ylide character of these transition states bears on these issues. Breslow has argued eloquently that demonstrable anions need not lie on the mechanistic sequence of an elimination reaction[21]; conceivably the converse principle may apply to the cleavage of I. Although too unstable to appear as a discrete intermediate, an ylide possibly can modify the character and lower the energy of structurally related transition states.

[21] R. Breslow, *Tetrahedron Letters* No. 8, 399 (1964).

[22] E. S. Lewis and M. D. Johnson, *J. Am. Chem. Soc.* **81**, 2070 (1959).

ion as the product-contributing species. However, if both III and XII are reactive electrophiles, the ambiguity arises that the terms k_1 [HOAc] [III] and k_2 [OAc$^-$] [XII] are kinetically indistinguishable, and the reaction may be given the interpretation that VIII is formed by combination of XII with water, while IX results from combination of XII with acetate ion and of III with acetic acid.[23]



Although the postulation of a reaction between III and acetic acid is consistent with the recent investigations of DeTar on the related reaction of carbodiimides with carboxylic acids in aprotic solvents,[24] the selectivity required for such a contribution in the benzoketoketenimine system is prohibitively high, for the form of the competition data require that reaction of III with water cannot contribute significantly to the formation of N-ethylsalicylamide, and therefore that III must be at least an order of magnitude more discriminatory than the combination of III and XII. Since the overall system is one of the most selective electrophiles known, contribution from reaction of III with acetic acid seems unlikely, and product formation is best viewed as involving water and acetate ion as the reactive nucleophiles.

On a molecule for molecule basis, acetate ion is 2 × 10^4 times more reactive than water toward the ketoketenimine electrophile, a factor which may be compared with 7·2 × 10^3 which Swain and Scott observed for the competition of acetate and water for benzoyl chloride, the most selective electrophile observed in their study of relative reactivity.[25]

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[23] For the general case of reaction of III and XII with water, hydroxide, acetate, and acetic acid, the function F[H$^+$] of equation (6) has the form shown in (7), where primed terms refer to reaction with XII; K_x, K_w, and K_a are the respective dissociation constants of XII, water, and

$$F([H^+]) = \frac{k_wK_x + k_w'[H^+] + k_1K_x[OH^-] + k_1'K_w}{k_2K_x + k_2'[H^+] + k_3\frac{K_x}{K_a}[H^+] + \frac{K_3'}{K_a}\cdot[H^+]^2} \qquad (7)$$

acetic acid; and k_w, k_1, k_2 and k_3 refer respectively to reaction with water, hydroxide, acetate, and acetic acid. The requirement of invariance reduces this expression either to case (a), or to the more interesting case (b) discussed in the text.

$$\text{(a)}\quad F([H^+]) = \frac{k_w + k_1'\frac{K_w}{K_x}}{k_2} \qquad \text{(b)}\quad F([H^+]) = \frac{k_w'}{k_2' + k_3\frac{K_x}{K_a}}$$

[24] D. F. DeTar and R. Silverstein, *J. Am. Chem. Soc.* **88**, 1020 (1966).

[25] C. G. Swain and C. B. Scott, *J. Am. Chem. Soc.* **75**, 141 (1953).

Qualitative experiments with azide and cyanate ions indicate that these nucleophiles are respectively about 25 and 0·5 times as reactive as acetate toward the benzoketoketenimine species. Thiourea, on the other hand, appears to be about an order of magnitude less reactive than acetate. This result is in accord with the known sluggish behavior of second row nucleophiles toward unsaturated electrophiles, and in this connection it is worth noting that thiocyanate combines with I as a nitrogen rather than as a sulfur nucleophile.[2]

The high selectivity of this extraordinarily reactive electrophile merits notice, and while the origin of the effect is unclear, it yields the important practical consequence that O-acyl-N-ethylsalicylamides can be prepared in high yield by combination of the N-ethylbenzisoxazolium cation with aqueous solutions of carboxylic acid salts.

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