

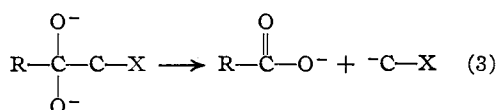
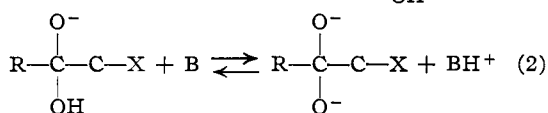
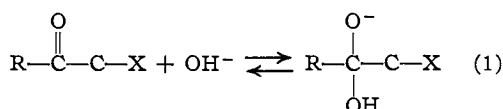
[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY, NORTHWESTERN UNIVERSITY]

Mechanism of the Hydrolytic Cleavage of Carbon-Carbon Bonds. III. Hydrolysis of α -Nitro and α -Sulfonyl Ketones¹BY RALPH G. PEARSON, DAVID H. ANDERSON AND LESLIE L. ALT²

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The alkaline hydrolysis of an α -sulfonyl ketone requires two moles of hydroxide ion per mole of ketone in the rate-determining step. The hydrolysis of an α -nitro ketone in alkali requires only one mole of hydroxide ion, and in water the hydrolysis requires the removal of only one hydrogen ion. The stability of the carbanion which is formed in the hydrolysis of an activated ketone determines the rate behavior with changing pH.

In previous studies^{1,3} it was shown that the alkaline hydrolysis of certain negatively substituted ketones requires the reaction of two hydroxide ions (or one hydroxide ion and one molecule of other base B) with one molecule of ketone in the rate determining step. The following mechanism was proposed



If steps 1 and 2 are equilibria and 3 is slow then the rate equation will be

$$\text{rate} = k[\text{ketone}][\text{OH}^-]^2 \quad (4)$$

which has been observed in the case of 2-ketoalkylpyridinium salts.³ If 1 is an equilibrium and 3 is rapid, reaction 2 becomes rate determining and general base catalysis is found

$$\text{rate} = [\text{ketone}][\text{OH}^-] \sum_i k_i[\text{B}_i] \quad (5)$$

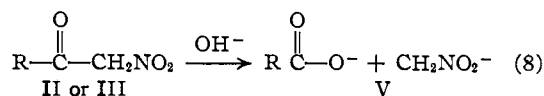
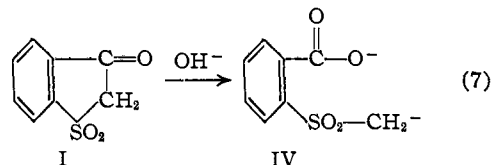
where k_i is the catalytic constant for each base B_i . Expressions such as 5 have been observed for the alkaline hydrolysis of chloral hydrate,⁴ acetylacetone and α -methylacetylacetone.¹ If 1 is slow and 2 and 3 are rapid, the reaction shows specific hydroxide ion catalysis and the rate equation is

$$\text{rate} = k[\text{ketone}][\text{OH}^-] \quad (6)$$

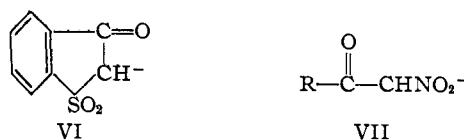
Such a rate expression has been found for α, α -dimethylacetylacetone.¹

Since it was felt that the stability of the carbanion formed in step 3 would determine whether this step would be fast or slow, kinetic studies have been made of the alkaline hydrolysis of 3-ketodihydrobenzothiophene 1-dioxide (I) and on the alkaline and neutral hydrolysis of nitroacetone (II) and ω -nitroacetophenone (III). The sulfonyl ketone on cleavage would form a rather unstable

carbanion IV whereas the nitro ketone would form a very stable carbanion V, that of nitromethane.



As in previous cases studied the ketones are pseudo-acids of sufficient strength so that the initial rapid reaction with alkali produces the carbanions VI and VII.



Because of double bond character in the bonds to be cleaved, these carbanions are assumed resistant to further attack by alkali, and it is only the neutral ketones in equilibrium with them which are cleaved.

Experimental

3-Ketodihydrobenzothiophene 1-dioxide was kindly supplied by Professor F. G. Bordwell and recrystallized from hot ethanol (m.p. 132-133°). Nitroacetone was prepared by Dr. May Nilson⁵ and was crystallized from ethyl ether (m.p. 46-47°). This compound was kept under ether in a refrigerator because of its instability. Nitroacetophenone was prepared and purified by Dr. W. B. Brownell (m.p. 107°).⁶

In the case of the sulfonyl ketone it was found that the product gave no polarographic wave whereas the starting material gave a well defined one in acetic acid-acetate buffer with a half-wave potential at -0.92 volt. Thus the polarographic method was used to study the rate of hydrolysis.

Reaction mixtures of the ketone in water and of aqueous sodium hydroxide containing approximately 10^{-3} M ketone were kept at $25 \pm 0.05^\circ$. Two-ml. samples were withdrawn and diluted to 20 ml. with an acetate-acetic acid buffer of pH 4. Under these conditions hydrolysis is stopped, and the diffusion current was shown by separate tests to be proportional to the concentration of sulfonyl ketone.

The sample was degassed by passing through nitrogen saturated with water vapor and the polarogram taken with a Sargent Recording Polarograph, Model XXI. The drop time and drop mass of the mercury were checked for constancy from time to time. The data were plotted as for a

(1) For previous papers see THIS JOURNAL, **73**, 926, 930 (1951).
 (2) Abstracted in part from M.S. thesis of L. L. Alt, Northwestern University, 1952.
 (3) R. G. Pearson and R. L. Dillon, THIS JOURNAL, **70**, 1933 (1948).
 (4) C. Gustafsson and M. Johanson, Acta Chem. Scand., **2**, 42 (1948).

(5) M. Nilson, Ph.D. thesis, Northwestern University, 1951.
 (6) W. B. Brownell, Ph.D. thesis, Northwestern University, 1949.

first-order reaction, $\log I_0/I$ vs. the time where I_0 is the initial diffusion current, I the current at time t . I_∞ was shown to be zero. Good linearity for the first-order plots was observed and the pseudo first-order constants calculated are shown in Table I.

TABLE I
ALKALINE CLEAVAGE OF 3-KETODIHYDROBENZOTHIOPHENE
1-DIOXIDE, WATER 25°

| Ketone, $M \times 10^3$ | Base, $M \times 10^3$ | $k_{\text{obsd.}}$, $\text{min.}^{-1} \times 10^3$ | kK_1 , min.^{-1} |
|----------------------------|--------------------------|--|--------------------------------|
| 1.08 | 2.152 | 1.78 | 1.66 |
| 0.990 | 2.990 | 2.68 | 1.34 |
| 1.140 | 6.840 | 8.79 | 1.54 |
| 0.990 | 10.89 | 16.4 | 1.66 |
| 1.50 | 1.07 | Zero ^a | .. |

^a After 12 days no change observed.

For the nitro ketones the polarographic method failed since the product nitromethane has nearly the same wave as the starting ketone, the half-wave potentials being nearly identical in the case of nitroacetone which was investigated in some detail.

The constancy of the diffusion current under conditions where extensive hydrolysis had occurred is the best proof we have that nitromethane is indeed a product of the reaction. It is easy to isolate very high yields (90%) of benzoic acid from the alkaline hydrolysis of nitroacetophenone but the isolation of nitromethane failed presumably because of the instability of nitromethane in aqueous solution over the long times required for cleavage of the nitro ketone. No reference to the formation of nitromethane from the hydrolysis of nitroketones could be found in the literature, but bromo-nitromethane has been found in the cleavage of 1-bromo-1-nitroacetone.⁵ The alkaline cleavage of 3-ketodihydrobenzothiophene 1-dioxide has been reported to give a 90% yield of *o*-methanesulfonylbenzoic acid, the expected product from IV.⁷

The carbanion, VII, absorbs strongly in the ultraviolet with a peak near 350 $m\mu$ for nitroacetophenone and 320 $m\mu$ for nitroacetone. The initial products of cleavage are transparent in this region. Accordingly the rates were studied by using a Beckman DU spectrophotometer to measure the optical density at the maxima as a function of time. Reaction mixtures were made as before except that the nitroacetophenone had to be dissolved in purified dioxane prior to adding to water or aqueous alkali. The final solutions contained 4% of dioxane by volume. The ketone concentration was only about $10^{-4} M$ because of the low solubility. For reading the optical density, samples were diluted tenfold with $10^{-4} M$ sodium hydroxide. The data were plotted as pseudo first order, $\log D_0/D$ vs. the time. The optical density at the end of the reaction was found to be zero except as noted in the next section.

It was found that nitroacetone gave good first-order kinetics in solutions containing low concentrations of alkali but that high concentrations of alkali caused an apparent decrease in the first-order constant. Since the optical density did not go to zero at long times, it was concluded that nitromethane, unstable in strong alkali, was forming products which absorbed at 320 $m\mu$. Rate constants were obtained for nitroacetone only over a limited range of hydroxide ion concentrations because of this. For nitroacetophenone this difficulty was not observed, the optical density going to zero in the strongest alkali used which was, however, only $10^{-3} M$. Apparently the decomposition products do not absorb strongly at 350 $m\mu$.⁸ Good first-order constants were obtained which are shown in Table II.

In the case of the nitro ketones it was found that cleavage occurred readily in pure water, in fact, much more rapidly than in alkali. The rate did not follow a first-order law, however, the apparent rate constant in the case of nitroacetophenone decreasing by a factor of two over a time of one half-life. Since it was found that hydrogen ion inhibits the cleavage, this slowing down can be attributed to

(7) A. W. Weston and C. M. Suter, *THIS JOURNAL*, **61**, 389 (1939).

(8) The anion of methazonic acid which is formed from nitromethane in strong alkali is reported to have strong absorption at 2980 Å.; C. M. Drew, J. R. McNesby and A. S. Gordon, *THIS JOURNAL*, **76**, 3098 (1954).

increased hydrogen ion produced during the hydrolysis. Initial first-order constants (10% reaction) were calculated and are shown in Table II.

The ionization constant of ω -nitroacetophenone was found by preparing buffer solutions with alkali containing 4% dioxane and measuring the initial pH with a model G Beckman pH meter. Neglecting activity coefficients $K_a = 6.4 \times 10^{-8}$. The ionization constant of benzoic acid determined in the same medium was found to be 5.8×10^{-5} . A calculation shows that if nitroacetophenone is half-hydrolyzed in water to benzoic acid, the hydrogen ion concentration will increase by a factor of 2.2.

The ionization constant of nitroacetone has been previously⁹ found to be 9×10^{-6} . Since acetic acid has $K_a = 1.8 \times 10^{-5}$ a calculation shows only a 22% increase in hydrogen ion concentration at the half-life for cleavage. In agreement with this, 15–20% decreases in apparent first-order constants were observed in the hydrolysis of nitroacetone in pure water up to the half-life.

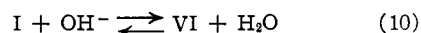
Since the initial absorption spectrum of the nitro ketones was independent of alkali (up to $10^{-3} M$) after one equivalent of base had been added, it was concluded that they function only as monobasic acids. The acid ionization constant of 3-ketodihydrobenzothiophene 1-dioxide has been reported previously as 2.2×10^{-8} and no evidence was found for a second stage of ionization.¹⁰

Discussion

It is clear from Table I that the sulfonyl ketone cleaves with a rate given by equation 4. Because of the initial formation of VI, the rate becomes

$$\text{rate} = kK(a - x)[OH^-] \quad (9)$$

where $(a - x)$ has its usual meaning and $1/K$ is the equilibrium constant for the reaction



and is equal to K_a/K_w or 2.2×10^6 . The pseudo first-order constant is then $kK[OH^-]$. The data in Table I are in good agreement with the direct proportionality to remaining hydroxide ion, remembering that the ketone uses up one mole of hydroxide ion, as in 10, instantaneously. Also the rate goes to essentially zero when the hydroxide ion is repressed to low values by having an excess of ketone. We can therefore conclude that the cleavage of the sulfonyl ketone probably involves the rapid establishment of steps 1 and 2 and a slow, rate-determining cleavage as in 3. This is as expected because of the low stability¹¹ of the carbanion IV which is formed in step 3.

The effect of pH on the rate of cleavage of the two nitro ketones as shown in Tables II and III, is very similar in regions where the experiments overlap and it may be concluded that the mechanism and rate laws are the same for both, with somewhat different constants involved. The results for nitroacetophenone in excess base shows there is no term corresponding to two hydroxide ions reacting with one mole of ketone in the kinetics, the rate being given by equation 6, which becomes in this case

$$\text{rate} = kK(a - x) \quad (11)$$

The pseudo first-order constant is thus independent of hydroxide ion concentration as is seen in Table III.

(9) R. G. Pearson and R. L. Dillon, *ibid.*, **75**, (1953).

(10) G. Schwarzenbach and E. Felder, *Helv. Chim. Acta*, **27**, 1701 (1944).

(11) For a comparison of the acid strengthening influence of various negative groups see reference 9. There is an error in Table IV of this reference in that compound 32 should read $CH_3COCH_2SO_3CH_3$.

TABLE II
CLEAVAGE OF NITROACETONE IN WATER AT 50°

| Ketone, $M \times 10^3$ | Base, $M \times 10^3$ | $k_{\text{obsd.}}, \text{min.}^{-1} \times 10^4$ |
|-------------------------|-----------------------|--|
| 1.047 | 2.094 | 8.70 |
| 0.998 | 0.998 | ~20 |
| 0.998 | 0.666 | 62.2 |
| 2.018 | 1.009 | 48.3 |
| 3.045 | 1.015 | 35.7 |
| 1.009 | None | 11.2 ^a |
| 2.018 | None | 7.8 ^a |
| 3.027 | None | 6.9 ^a |

^a Initial rates only.

TABLE III
CLEAVAGE OF ω -NITROACETOPHENONE IN 4% DIOXANE-WATER AT 25°

| Ketone, $M \times 10^3$ | Base, $M \times 10^3$ | $k_{\text{obsd.}}, \text{min.}^{-1} \times 10^4$ |
|-------------------------|-----------------------|--|
| 7.83 | 7.83 | ~6 |
| 7.83 | 15.66 | 2.40 |
| 7.83 | 39.15 | 2.38 |
| 7.83 | 78.30 | 2.37 |
| 7.83 | None | 26 ^a |
| 19.70 | None | 12 ^a |
| 7.83 | 0.25 M HCl | Zero ^b |

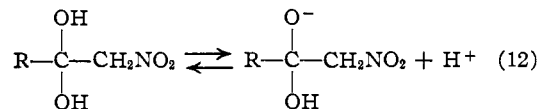
^a Initial rates only. ^b No change after 5 days.

It can be concluded then that in the case of the nitro ketones in excess alkali, the addition of hydroxide ion to the carbonyl group as in equation 1 is the rate-determining step. Steps 2 and 3 are rapid, the latter going easily because of the stability of the anion of nitromethane V. This supposed mechanism is given extra support by the results of Cook and Taft¹² on the cleavage of thenoyltrifluoroacetone in base. Since the CF_3CO and NO_2 groups are about equal in activating effect,⁹ very similar behavior can be expected for the compounds $\text{RCOCH}_2\text{COCF}_3$ and $\text{RCOCH}_2\text{NO}_2$. In the case of thenoyltrifluoroacetone, which can exist as the hydrate $\text{RC}(\text{OH})_2\text{CH}_2\text{COCF}_3$ as well as in the ketone form, it was found that putting the hydrate in aqueous base (above $p\text{H}$ 9) leads to very rapid, almost complete, cleavage. If the anhydrous ketone is put into base, however, a rapid acid-base neutralization occurs first followed by a slow cleavage. This behavior corresponds to step 1 being slow and steps 2 and 3 being rapid in our reaction scheme. Starting with the hydrate circumvents the slow step 1 since a rapid proton loss can give the product corresponding to reaction 1.

Although the nitro ketones are not reported to form stable hydrates, undoubtedly some hydrate formation occurs in neutral or acidic solution. The

(12) E. H. Cook and R. W. Taft, Jr., *THIS JOURNAL*, **74**, 6103 (1952).

ionization of the hydrate can then take the place of reaction 1 in the absence of alkali.



This equilibrium step followed by reactions 2 and 3 would then constitute the mechanism of cleavage of nitro ketones in acidic solution. The rate should be inversely proportional to the hydrogen ion concentration, if 2 is the slow step.

The data in Tables II and III bear out this prediction. The initial rate constants show a reasonable inverse relationship to the initial concentration of hydrogen ion as calculated from the ionization constants of the nitroketones. Furthermore the observed rate constants decrease with extent of reaction in accordance with an increased hydrogen ion concentration (see remarks in Experimental section). Finally the hydrolytic cleavage can be completely repressed in strong, mineral acid solution.

One cannot compare the rates in alkaline solution with those in acidic solution since quite different rate-determining steps are involved. It can be assumed that in sufficiently acid solutions, the rate of hydrate formation is rapid enough so that it is not rate determining. Hydrate formation of acetaldehyde is subject to both general acid and general base catalysis¹³ and the same may be assumed true for the nitro ketones.

In solutions of intermediate $p\text{H}$, near neutrality, the hydration of the ketone may become rate determining for the cleavage. The possibilities are too complex to sort out, but it can be predicted that a maximum rate of cleavage would be reached in a solution containing excess ketone (to form the hydrate) and still basic enough so that hydration followed by the loss of two protons as in 12 and in 2 would be rapid. This is borne out by the results of Table II which show a maximum rate of cleavage in a solution containing $2/3$ mole of base to one mole of ketone.

It was noticed that attempts to measure the rate for solutions containing equivalent amounts of nitro ketone and of base gave good first-order kinetics but duplicate runs would give rate constants differing by as much as 80%. This is due to the rather large acceleration in rate caused by a slight excess of nitroketone (see Table II). The approximate values given in Tables II and III are the lowest of those observed and may still be too high.

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(13) R. P. Bell and B. de B. Darwent, *Trans. Faraday Soc.*, **46**, 34 (1950).