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Mechanism of the Nitration of Furans. I. Conversion of the Nitration Intermediate Derived from Furfural into 5-Nitro-2-furfural Diacetate

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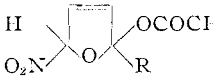
The kinetics for the conversion of the nitration intermediate derived from furfural into 5-nitro-2-furfural diacetate have been investigated. It has been shown that this conversion is in agreement with Brönsted's theory of general base catalysis.

It has long been known that simple furan compounds that contain no electronegative groups can be nitrated only by mixtures of acetic anhydride and nitric acid.[1-4] The work of Marquis,[1] Rinkes,[2] Gilman,[3] Johnson,[5] and Kimel, *et al.*,[4] has shown that, in many cases, the nitration reaction proceeds by the formation of a nitration intermediate which is subsequently converted to the nitrofuran by the action of a mild base. Various structures have been proposed for the nitration intermediate derived from furan by the above authors, but it was not until 1947 that Clauson-Kaas and Fakstorp[6] definitely concluded that its structure was that of 2-acetoxy-5-nitro-2,5-dihydrofuran (I), as suggested by Freure and Johnson.[4]



I, R = H
II, R = $CH(OCOCH_3)_2$

The appearance of such an intermediate represents the major difference between aromatic and furan nitrations. In the case of furfural, the nitration intermediate is a stable, crystalline, well-defined compound with an empirical formula of $C_{11}H_{13}NO_9$. This formula corresponds to a compound consisting of one molecule of nitrofurfural diacetate and one molecule of acetic acid. A recent study[7] indicates that the structure of this intermediate II is analogous to the one derived from furan (I).

It is known that furan nitration intermediates are converted into the nitrofurans by elimination of the elements of acetic acid. This conversion is readily brought about by organic bases such as pyridine and dimethylaniline[7] and by inorganic bases such as sodium carbonate, sodium acetate and ammonia.[4,7]

In the present investigation, the conversion of the intermediate derived from furfural (II) into 5-nitro-2-furfural diacetate was studied from a kinetic viewpoint. The rate of conversion of II was determined in a mixture of water, acetic acid and trisodium phosphate[4] at *p*H 3.7 by following the appearance of the ultraviolet absorption maximum of nitrofurfural diacetate. After taking precautions required by the light-sensitivity of nitrofurans, it was established that the kinetics were first order (or pseudo-first order) with respect to II. By the use of powdered Pyrex glass it was shown that the reaction is homogeneous, *i.e.*, is not surface catalyzed.

Next, the influence of *p*H on the rate of conversion was investigated. The results so obtained were conflicting until it was found that there was a pronounced "salt effect," *i.e.*, the electrolyte concentration, even of species other than catalysts and reactants, influences the rate. Runs were then made in solutions 0.1 molar or less to minimize this. This series, run in sodium acetate-acetic acid buffers, showed an increasing rate of reaction as the medium was made less acidic with a tremendous rate increase between *p*H 5.75 and 7.0. Below a *p*H of 2.75 the rate was exceedingly slow. Thus the rate was no simple function of *p*H or of acetate ion concentration throughout the range. It was also noted that at a constant *p*H, higher acetate ion concentrations gave a faster reaction.

Consideration was then given to possible mechanisms which would fit these observations.

Lack of acid catalysis eliminated the possibility of ester hydrolysis at the 2-acetoxy group, followed by dehydration. The kinetics appeared to be similar to those observed by Brönsted and Pedersen[8] for the decomposition of nitramide, $H_2N_2O_2$, to water and nitrous oxide. Here the mechanism has been established as a rate-controlling deprotonation, exhibiting general base catalysis, followed by a rapid dehydration to nitrous oxide

$$O_2NNH_2 + B^{\ominus} \rightleftarrows BH + O_2N\overset{\ominus}{N}H$$
$$O_2N\overset{\ominus}{N}H \longrightarrow OH^{\ominus} + N_2O$$
$$BH + OH^{\ominus} \rightleftarrows B^{\ominus} + H_2O$$

This was the kinetic study with which Brönsted developed the concept of general base catalysis.

The concept of an initial, rate-controlling deprotonation step in the case of the nitration intermediate seemed especially attractive due to the possible stabilization of the carbanion formed by the multiplicity of resonance forms possible.

Such a mechanism is responsible for the acidity of the nitro-aliphatics[9] and since the dihydrofuran ring is planar such resonance stabilization is possible here. Even at best, carbanions are very unstable so the spontaneous loss of acetate ion is probably very rapid and not rate controlling.

Working on this postulated mechanism, consideration was then given to the nature of basic species present in the acetic acid-sodium acetate buffer systems employed. The more basic species are hydroxyl and acetate ions. Calculations of their

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(1) R. Marquis, *Compt. rend.*, **132**, 140 (1901); **134**, 776 (1902); *Ann. chim. phys.*, [8] **4**, 196 (1905).

(2) I. Rinkes, *Rec. trav. chim.*, **49**, 1169 (1930).

(3) H. Gilman and G. Wright, THIS JOURNAL, **52**, 2550 (1930).

(4) W. Kimel, J. H. Coleman and W. B. Stillman, U. S. 2,490,006 (1949).

(5) B. T. Freure and J. R. Johnson, THIS JOURNAL, **53**, 1142 (1931).

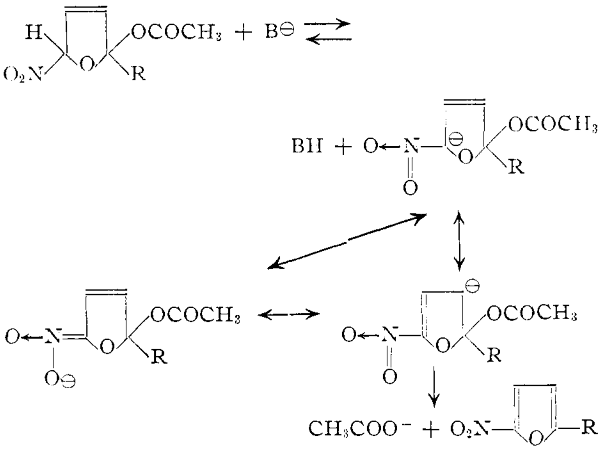
(6) N. Clauson-Kaas and J. Fakstorp, *Acta Chem. Scand.*, **1**, 210 (1947).

(7) R. Kimura, *J. Pharm. Soc. Japan*, **75**, 424 (1955); **75**, 1175 (1955).

(8) J. N. Brönsted and K. Pedersen, *Z. physik. Chem.*, **108**, 185 (1924).

(9) B. Turnbull and S. H. Maron, THIS JOURNAL, **65**, 212 (1943).

relative concentrations show a rapid increase in hydroxyl ion above a *p*H of 5.75. This coincides with the point of great rate increase. Thus, the observed rate of conversion is dependent on all the basic species present and may be expressed by the equation



$$k_0 = k_{OH^-}[OH^-] + k_{B_1^-}[B_1^-] + k_{B_2^-}[B_2^-] + \dots \quad (1)$$

where

k_0 = obsd. rate constant for conversion
k_{OH^-} = rate constant for conversion due to OH^-
$k_{B_1^-}$, $k_{B_2^-}$, etc. = rate constant for conversion due to B_1^-, B_2^-, etc.
$[OH^-]$, $[B_1^-]$, $[B_2^-]$, etc. = concn. of OH^-, B_1^-, B_2^-, etc.

The values for k_{OH^-}, $k_{B_1^-}$, etc., are dependent on the basic strength of the respective anions. The higher the basic strength, *i.e.*, the greater the tendency for the anion to take on a proton, the greater the individual rate constants will be. Thus, in the present case, the hydroxyl ion is a much stronger base than the acetate ion and k_{OH^-} will be much greater than k_{OAc^-}. Up to a *p*H of 5.75, the first term of equation 1—k_{OH^-} $[OH^-]$— is very small because $[OH^-]$ is very small, and the rate of the conversion will change relatively slowly with changing *p*H. From *p*H 5.75 to 6.75 both hydroxyl and acetate ions contribute to the rate. Above *p*H 6.75, k_{OAc^-}·$[OAc^-]$ becomes negligible with respect to the tremendous increases in k_{OH^-}-$[OH^-]$ and a small *p*H change will greatly affect the rate.

In order to verify the hypothesis of general base catalysis in the conversion of II, basic species other than acetate were used. Buffer systems containing equal moles of various acids and their sodium salts were prepared. The *p*H of such solutions is, by definition, the pK_a of the acid used. Duplicate runs were made in each buffer. The results obtained are shown in Fig. 1 and are summarized in Table I. In all runs, the temperature was 30.00 ± 0.05° and the concentration of intermediate 10.0 mg./l.

Table I

Buffer system	*p*H	[Acid] = [Salt] (mole/l. × 10^2)	k_0 (sec.$^{-1}$ × 10^5)
Trimethyl acetate	4.97	2.72	8.01
Acetate	4.76	2.58	4.83
Phenyl acetate	4.24	2.49	2.57
Benzoate	4.16	1.29	1.03
Formate	3.65	2.44	0.875
Furoate	3.13	4.12	0.684

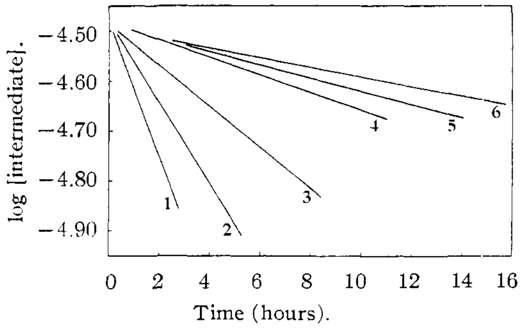


Fig. 1.—Rate of conversion of furfural nitration intermediate with various buffers: 1, trimethylacetate; 2, acetate; 3, phenylacetate; 4, benzoate; 5, formate; 6, furoate.

When log k_0/C (where C is the concentration of the anion) is plotted against log K_B for these runs, the straight line of Fig. 2 is obtained. The linearity of this relationship between k_0 and log K_B agrees with the theory that the conversion of II to nitrofurfural diacetate is a reaction that fits Brönsted's general base-catalyzed type.

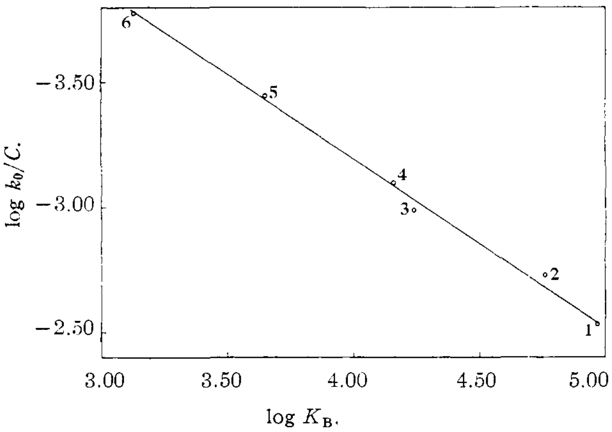


Fig. 2.—Relation between rate of conversion and basic strength of various anions: 1, trimethylacetate; 2, acetate; 3, phenylacetate; 4, benzoate; 5, formate; 6, furoate.

The constants for this line, given in terms of Brönsted's general base catalysis equation[8]

$$\log \frac{k_B}{q} = \beta \log \frac{p}{q} K_B + \log G_B$$

are

$$p = q = 1, \beta = 0.676, G_B = 1.26 \times 10^{-6}$$

An attempt was next made to determine the values for k_{OH^-} and k_{B^-} in equation 1 by holding the *p*H constant and varying the concentration of B. This was carried out by successive dilutions of the trimethylacetic acid–sodium trimethylacetate buffer used in Table I. The total ionic strength was maintained constant by the addition of the necessary amounts of potassium chloride. The results obtained are shown in Fig. 3 and Table II. In all cases, the temperature was 30.25 ± 0.05° and the concentration of intermediate 10.0 mg./l.

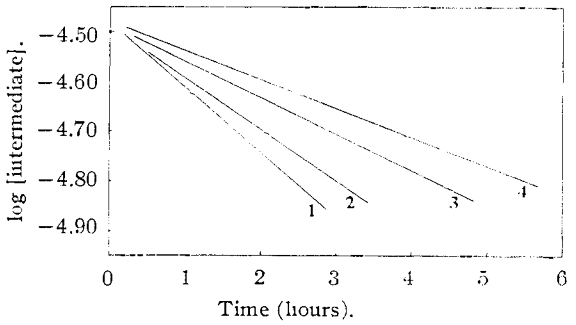


Fig. 3.—Rate of conversion of furfural nitration intermediate at various concentrations of trimethylacetate buffer at *p*H 4.97. [Acid] = [Salt]: (1) 2.72×10^{-2} mole/l.; (2) 2.04×10^{-2} mole/l.; (3) 1.36×10^{-2} mole/l.; (4) 1.09×10^{-2} mole/l.

By plotting k_0 against the concentration for these runs, the straight line represented by

$$k_0 = 2.68 \times 10^{-3}\,C + 7.19 \times 10^{-6}$$

is obtained. The slope of this line is k_{B^-} for trimethylacetate ion. From the slope, or from the intercept, k_{OH^-} was calculated as 7700 l./mole-second. This value for k_{OH^-} cannot be considered accurate since a very small error in k_{B^-} is greatly magnified in calculating k_{OH^-}. However, it can serve as a basis for comparison of the various k_{B^-}'s. These calculated values are shown in Table III.

TABLE II

TRIMETHYLACETATE BUFFER, *p*H 4.97

[Acid] = [Salt] (mole/l. × 10^2)	[KCl] (mole/l. × 10^2)	k_0 (sec.$^{-1}$ × 10^5)
2.72	0	8.01
2.04	1.36	6.52
1.36	2.72	4.62
1.09	3.26	3.53

Experimental

Preparation of Furfural Nitration Intermediate (II).—The nitration of furfural was carried out according to the method of Kimel, Coleman and Stillman.[4] Instead of converting the reaction mixture directly to 5-nitro-2-furfural diacetate as described, it was poured into ice and water and stirred 1.5 hr. The aqueous solution was decanted and the sticky residue was triturated with warm ether, then chilled in ice. The solids were filtered and washed twice by slurrying with ether. After drying at 60°, the crude product (28.5%) melted at 101–103.5°. Recrystallization from dry benzene (85% recovery) raised the melting point to a maximum of 107–108°.

TABLE III

Anion B^-	k_{B^-} (l./mole sec.)
Trimethylacetate	2.68×10^{-3}
Acetate	1.70×10^{-3}
Phenylacetate	9.80×10^{-4}
Benzoate	7.13×10^{-4}
Formate	3.44×10^{-4}
Furoate	1.64×10^{-4}

Temperature = 30.25 ± 0.05°

Preparation of Buffer Solutions.—Trimethylacetic acid was fractionated *in vacuo* and a 10-g. sample boiling at 85.5–86° at mm. collected. This material titrated 98.8%.

Reagent grade acetic acid was used as received.

Phenylacetic acid was recrystallized to a constant melting point of 76–77°.

NBS acidimetric sample of benzoic acid was used as received.

Reagent grade formic acid was used as received.

Furoic acid was purified by dissolving in sodium bicarbonate, treating with Darco, reprecipitating with acid and recrystallizing from water. It titrated 99.2%.

With the phenylacetic, furoic and benzoic acids, weighed amounts were dissolved or suspended in water and treated with 0.5 equivalent of standard 1 *N* sodium hydroxide then diluted to volume. With the trimethylacetic, acetic and formic acids, standardized 0.1 *N* solutions of the acids were treated with 0.5 equivalent of standard 1 *N* sodium hydroxide. In all cases, the amount of free acid in the buffers was checked by titration.

Kinetic runs were carried out as follows. Samples of nitration intermediate II of about 1 mg. were weighed to the nearest microgram in a 1-ml. beaker and dissolved in 0.2 ml. of pure, dry tetrahydrofuran. This sample was added to the buffer solution (100 ml. of buffer per mg. of sample) contained in a glass-stoppered low-actinic flask. Samples were withdrawn periodically and the absorption at 3080 Å read directly in a Beckman Model DU spectrophotometer. From the absorptions read, these several calculations were made: (1) concentration of nitrofurfural diacetate (mole/l.), obtained by dividing the absorbance by 10,950, the molecular absorption constant for nitrofurfural diacetate. (2) Concentration of II (mole/l.), obtained by subtracting (1) from 3.30×10^{-5}, the number of moles/liter of II at zero time. A plot of the log of the concentration of II against time was made and the best straight line drawn. The slope of this line, when multiplied by 2.303, gave the rate constant, k_0, in sec.$^{-1}$.

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