Mechanism of Nitric Acid Oxidation of Acetophenone to Dibenzoylfurazan 2-Oxide, Benzoic Acid, and Benzoylformic Acid

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Acetophenone, benzoylformaldehyde oxime, and benzoylnitromethane were oxidised with dilute nitric acid to dibenzoylfurazan 2-oxide, benzoic acid, and benzoylformic acid in aqueous organic solvents. The nitric acid oxidation of benzoylnitromethane in 78% aqueous nitromethane gave dibenzoylfurazan 2-oxide in *ca.* 70% yield, suggesting nitrosation of benzoylnitromethane to give nitrobenzoylformaldehyde oxime (benzoylformonitrolic acid). Similarly, acetophenone is considered to be attacked by the nitrosonium ion to give benzoylformaldehyde oxime, instead of benzoylnitromethane by nitration with nitrogen dioxide. Benzoylformic acid and benzoic acid are derived from the nitrolic acid and its oxidation product.

It is known that acetophenones are oxidised by nitric acid to give furazan 2-oxides,[1] and the reaction has often been used as a convenient preparative method for various kinds of diacylfurazan 2-oxides.[2] However, the detailed reaction mechanism remains to be studied. Snyder and Boyer[1] suggested benzoylformaldehyde oxime rather than benzoylnitromethane as an intermediate in the nitric acid oxidation of acetophenone, because dibenzoylfurazan 2-oxide was formed, in yield substantially lower than that obtained from acetophenone, when benzoylnitromethane was treated under the conditions employed with acetophenone. However, it was found in the present study that the nitric acid oxidation of benzoylnitromethane gave an amount of dibenzoylfurazan 2-oxide comparable with that obtained from acetophenone. It is known that furazan 2-oxides are obtained from nitrolic acids.[3] Benzoylformonitrolic acid which is a presumed intermediate in the present oxidation may be formed not only by way of benzoylformaldehyde oxime but also benzoylnitromethane, as will be described below. Hence, the possible intermediacy of benzoylnitromethane in the nitric acid oxidation of acetophenone should not be so easily discounted. Moreover, the reaction proceeds heterogeneously under the conditions reported,[1] which seems unsuitable for a discussion of mechanism. Almost no attention has been paid to the mechanism of formation of the carboxylic acids which are regarded as the main factor in reducing the yield of dibenzoylfurazan 2-oxide. In this paper, the detailed mechanism on the nitric acid oxidation of acetophenone is suggested based on experiments conducted under homogeneous conditions in aqueous dioxane, aqueous acetic acid, and aqueous nitromethane.

Results and Discussion

Nitric Acid Oxidation of Acetophenone.—Products. Acetophenone was easily oxidised to give the products (listed in Table 1) by dilute nitric acid containing a small amount of sodium nitrite in various solvents at 60 °C. Without sodium nitrite, the reaction was not initiated. All the reactions could be carried out in a homogeneous system. As shown in Table 1, the yield of dibenzoylfurazan 2-oxide (**13**) decreased, and those of carboxylic acids increased, as the content of water in the solvent increased. The formation of benzoic acid has already been reported in the nitric acid oxidation of acetophenone in a heterogeneous system[1,4] but in addition to that, the formation of an appreciable amount of benzoylformic acid was found under the present conditions.

Rate law. The oxidation rate of acetophenone using sodium nitrite as an initiator was followed by measurement of the amount of consumed acetophenone. The reaction rate was found to obey first-order kinetics with acetophenone in excess of nitric acid solution:

$$v = k_1[\mathrm{PhCOMe}]$$

The reaction was accelerated as the acidity of the media increased, and the plot of $\log k_1$ *versus* $-H_0$ (Hammett's acidity function) gave a straight line with a slope of 0.9 (Figure). The reaction rate constants at various nitric acid concentrations are shown in Table 2. Almost identical rates were observed when they were corrected to the same acidity ($H_0 = 0$). Hence, the oxidation rates depend on the acidity of the medium and they are independent of nitric acid concentration.

In the nitric acid oxidation of benzaldehyde, the rate is also independent of nitric acid concentration, but the rate was

Table 1. Yields of products from nitric acid oxidation of acetophenone in various solvents for 60 min at 60 °C. Initial concentration: $[NaNO_2]$ = 0.02M, [PhCOMe] = 0.0987M

		Products (%)		
$[HNO_3]$/M	Solvent	Furazan 2-oxide	Benzoic acid[a]	Benzoylformic acid[a]
3.74	50% Dioxane	25.3	47.3	25.4
3.74[b]	70% Dioxane	53.0	24.4	19.9
2.67	50% AcOH	42.3	34.6	21.7
2.67	70% AcOH	56.3	21.7	19.7
2.67	78% $MeNO_2$	68.3		

[a] The values were determined as the methyl ester with diazomethane. [b] The reaction was allowed to continue for 158 min.

Table 2. First-order rate constants in 70% dioxane solvent for various nitric acid concentrations at 60 °C. Initital concentration: $[NaNO_2]$ = 0.02M, $[H_2SO_4]$ = 2.0M, $[PhCOCH_3]$ = 0.10M

$[HNO_3]$/M	$10^4 k_1/s^{-1}$	$10^4 k_{1corr}/s^{-1}$[b]	H_0[c]
3.74[a]	23.5	5.50	−0.70[d]
3.74[a]	6.47	5.70	−0.06
0.267	4.00	5.45	+0.15
0.543	11.2	5.65	−0.33
0.802	15.2	5.38	−0.50
1.07	20.0	5.13	−0.66

[a] No sulphuric acid is added. [b] The values were corrected to the same acidity, $H_0 = 0$, according to the equation: $\log k_1$ corr = $\log k_1 + 0.9 H_0$. [c] Hammett's acidity function. [d] The reaction was conducted in 50% aqueous dioxane.

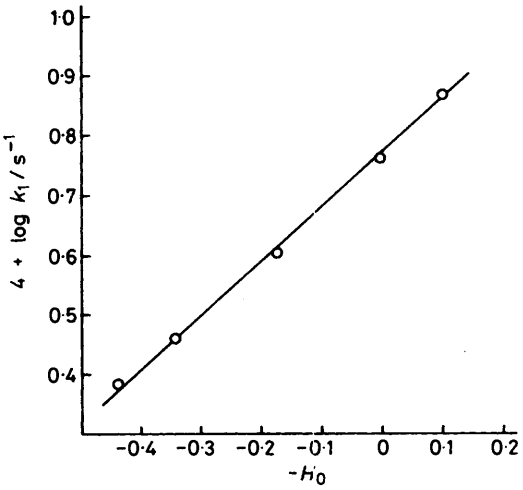


Figure. Plot of log k_1 *versus* $-H_0$ for the nitric acid oxidation of acetophenone in 70% dioxane at 60 °C. Initial concentration: [PhCOMe] = 0.0987M, $[HNO_3]$ = 2.67M, $[NaNO_2]$ = 0.02M, and $[H_2SO_4]$ = 0—0.8M

accelerated in the solvents containing a higher concentration of dioxane because of a higher content of nitrogen dioxide in the system.[5] However, in the present reaction, Table 2 indicates that the oxidation rate is independent of the solvent composition, and depends only upon the acidity of the medium. Hence, the first-order rate constant, k_1, does not include the effect of nitrogen oxides derived from nitric acid and nitrous acid. Furthermore, Table 3 indicates a rate enhancement by the electron-attracting group and a rate retardation by the electron-releasing group. The above results are explicable by assuming that the present reaction involves the enolisation of acetophenone and that the conjugate acid of acetophenone undergoes a rate-determining deprotonation.[6] Nitric acid reacts with nitrous acid to form dinitrogen tetraoxide. The dissociation constant of dinitrogen tetraoxide shows that it should dissociate almost completely either to nitrogen dioxide or to the nitrosonium and the nitrate ions, according to equations (1) and (2).[7] Generally, the attacking species in the

$$HNO_3 + HNO_2 \rightleftharpoons N_2O_4 + H_2O \quad (1)$$

$$2\,NO_2 \rightleftharpoons N_2O_4 \rightleftharpoons NO^+ + NO_3^- \quad (2)$$

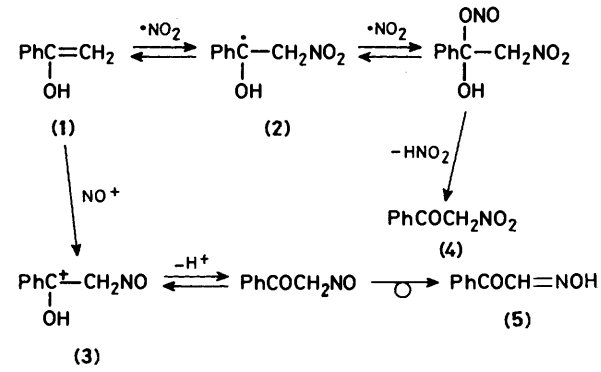
nitric acid oxidation are assumed to be nitric acid,[8] the nitrosonium ion,[9] nitrogen dioxide,[5] and nitrous anhydride.[1] However, nitric acid cannot be the attacking species, because it was found that the oxidation is not initiated in the absence of nitrous acid. In excess of nitric acid, nitrous acid should give nitrogen dioxide and the nitrosonium and the nitrate ions rather than its anhydride according to equations (1) and (2).[7] Therefore, one can consider a mechanism which involves both nitrogen dioxide and the nitrosonium ion as the attacking agents when sufficient amounts of these species are present.

Nitric Acid Oxidation of Benzoylformaldehyde Oxime and Benzoylnitromethane.—An appreciable amount of the furazan 2-oxide (**13**) was obtained in the oxidation of benzoylnitromethane (**4**) under the present conditions. This result differs from that reported by Snyder and Boyer.[1] Although benzoylnitromethane (**4**) was considered to be the oxidation product of α-nitrosoacetophenone,[1,4] it may be formed by an attack of nitrogen dioxide on the enol form of acetophenone, since it was found that the present oxidation involves the

Table 3. First-order rate constants in nitric acid oxidation of substituted acetophenones in 70% AcOH at 60 °C. Initial concentration: [ArCOMe] = 0.10M, $[NaNO_2]$ = 0.02M, $[HNO_3]$ = 1.33M

Substrate	$10^4\,k_1/s^{-1}$
p-$MeOC_6H_4COMe$	0.917
PhCOMe	2.88
p-$NO_2C_6H_4COMe$	4.58

enolisation of acetophenone, and nitrogen dioxide is known to add to olefins even at low temperature.[10] Alternatively, the enol (**1**) may be attacked by the nitrosonium ion to yield α-nitrosoacetophenone, which should isomerise to benzoylformaldehyde oxime (**5**) (Scheme 1). In order to determine a



Scheme 1.

probable intermediate in the oxidation of acetophenone, the nitric acid oxidation of benzoylnitromethane (**4**) and the oxime (**5**) was investigated under various conditions. The results are summarised in Table 4.

Effect of Nitrous Acid.—At first glance, it may appear that the oxidation of the oxime (**5**) proceeds in the absence of nitrous acid, because the furazan 2-oxide (**13**) and the carboxylic acids were obtained in considerable yields even in the presence of urea, an effective scavenger of nitrous acid (Runs 3 and 7). However, in the oxidation of the oxime (**5**), it was found that a considerable amount of nitrous acid began to accumulate in the system as the oxidation proceeded, even in the presence of urea under the above reaction conditions (Table 5). In the presence of a large amount of urea, the oxidation was obviously retarded (Run 4). When *p*-nitroaniline, a highly effective scavenger of nitrous acid,[11] was added to the system, the oxidation was completely suppressed (Run 5). Similarly, the oxidation of benzoylnitromethane (**4**) was also inhibited in the presence of a large amount of urea (Run 11). The above results indicate that neither the oxime (**5**) nor benzoylnitromethane (**4**) is attacked directly by nitric acid and the oxidation is initiated only with nitrous acid. Similar conclusions have been reported on nitric acid oxidation of other compounds.[5,12] Probably, the oxime (**5**) is reactive enough to compete with urea in the reaction with nitrous acid or nitrogen oxides (Run 3).

Nitrosation versus *Nitration of Benzoylnitromethane.*—Benzoylnitromethane will undergo enolisation more readily than acetophenone, due to the electron-withdrawing effect of the nitro group.[6] Unless the enol form of benzoylnitromethane

Table 4. Yields of products from nitric acid oxidation of benzoylformaldehyde oxime and benzoylnitromethane in various solvents for 30 min at 60 °C. Initial concentration: $[HNO_3]$ = 2.22M, [Substrate] = 0.0333M

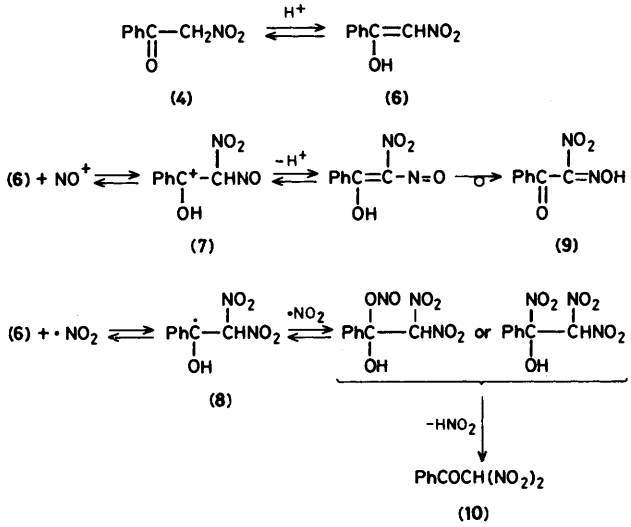
Run	Substrate	Additives (M)		Products (%) Furazan 2-oxide	Benzoic acid[a]	Benzoylformic acid[a]
1[b]	PhCOCH=NOH	$NaNO_2$	0.10	34.1	41.7	trace[e]
2[b]	PhCOCH=NOH	$NaNO_2$	0.10	55.9	19.1	21.1
3[b]	PhCOCH=NOH	$CO(NH_2)_2$	0.0336	55.9	19.1	21.2
4[b]	PhCOCH=NOH	$CO(NH_2)_2$	0.128	11.8	9.2	15.2
5[b]	PhCOCH=NOH	p-$NO_2C_6H_4NH_2$	0	0	0	0[f]
6[c]	PhCOCH=NOH	$NaNO_2$	0.10	53.8	20.5	20.2
7[c]	PhCOCH=NOH	$CO(NH_2)_2$	0.0381	58.9	11.8	16.0
8[d]	PhCOCH=NOH	$NaNO_2$	0.10	68.1	3.6	9.9
9[b]	$PhCOCH_2NO_2$	$NaNO_2$	0.10	31.4	40.6	trace[e]
10[b]	$PhCOCH_2NO_2$	$NaNO_2$	0.10	58.5	17.5	21.4
11[b]	$PhCOCH_2NO_2$	$CO(NH_2)_2$	0.13	0	0	0[f]
12[c]	$PhCOCH_2NO_2$	$NaNO_2$	0.10	56.2	21.6	17.7
13[d]	$PhCOCH_2NO_2$	$NaNO_2$	0.10	68.4	4.4	9.7
14[b]	$PhCOCHO \cdot H_2O$[g]	$NaNO_2$	0.10		trace	trace
15[c]	PhCOCOOH[h]	$NaNO_2$	0.10		trace	100

[a] The values were determined as a methyl ester with ethereal diazomethane. [b] The reaction was conducted in 70% dioxane. [c] The reaction was conducted in 70% acetic acid. [d] The reaction was conducted in 78% nitromethane. [e] The reaction was carried out at 26 °C. [f] The oxidation did not start even after 90 min. [g] The reaction was allowed to continue for 60 min. [h] The reaction was allowed to continue for 120 min.

Table 5. Variation of the concentration of nitrous acid in the system for nitric acid oxidation of benzoylformaldehyde oxime in 70% dioxane at 60 °C. Initial concentration: $[HNO_3]$ = 2.22M, [PhCOCH=NOH] = 0.0333M

Reaction time (min)	$[HNO_2]$/M	$[HNO_2]$/M
0	0[a]	0.100[b]
10	0.0090	0.0494
20	0.0120	0.0450
35	0.0140	0.0720
50	0.0190	0.0650
70	0.0190	0.0688
95	0.0200	

[a] 0.0336M Urea was added in place of sodium nitrite. [b] 0.100M Sodium nitrite was used as the initiator.



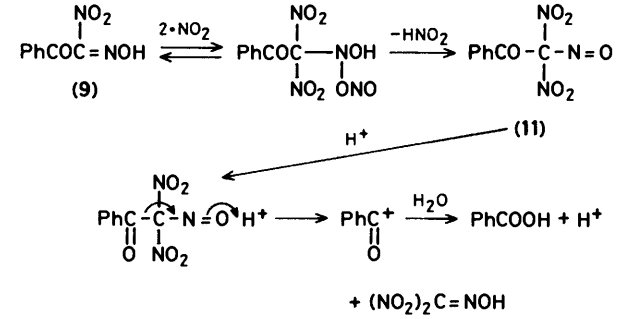
Scheme 2.

is attacked by the nitrosonium ion, the nitrolic acid (**9**), the intermediate to give the furazan 2-oxide (**13**), will not be formed. If the enol form of benzoylnitromethane is attacked by nitrogen dioxide, benzoyldinitromethane (**10**) should be formed. The enol form of benzoyldinitromethane (**10**) could be converted by nitrosation into αα-dinitro-α-nitrosoacetophenone (**11**), and so to benzoic acid (Scheme 3). The oxidation of benzoylnitromethane (**4**) gave the furazan 2-oxide (**13**) in *ca.* 56—58% yield in both 70% aqueous dioxane and 70% aqueous acetic acid (Runs 10 and 12), and the yield of the furazan 2-oxide (**13**) reached approximately 70% in 78% aqueous nitromethane (Run 13). Benzoic acid could be produced *via* two independent intermediates, *i.e.*, the nitrolic acid (**9**) and benzoyldinitromethane (**10**) as will be described below. However, the fact that benzoic acid was not formed in a higher yield than from the oxidation of the oxime (**5**) (Runs 2 and 10, or 6 and 12), would suggest that the pathway *via* benzoyldinitromethane (**10**) is not significant. Hence, it was concluded that benzoylnitromethane (**4**) is predominantly attacked by the nitrosonium ion to give the nitrolic acid (**9**).

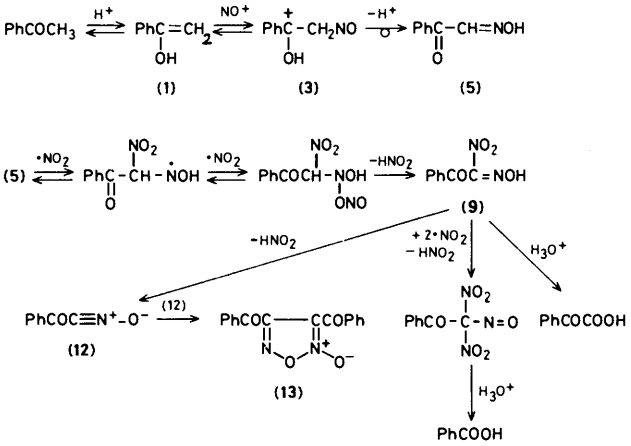
The Formation of Carboxylic Acids.—It may appear that benzoylformic acid and benzoic acid are formed *via* phenylglyoxal, which is formed by hydrolysis of the oxime (**5**). However, it was found that no measurable amount of the carboxylic acids was formed in the oxidation of phenylglyoxal monohydrate under the present reaction conditions (Run 14). Probably, benzoylformic acid is formed by hydrolysis of the nitrolic acid (**9**), similar to the case of benzonitrolic acid.[13] In the nitric acid oxidation of cyclohexanone, a similar nitrolic acid was suggested as an intermediate to adipic acid.[14]

$$PhCOC(NO_2)=NOH \xrightarrow[H_2O]{HNO_2} PhCOCOOH \qquad (3)$$

Benzoic acid is formally an oxidation product of benzoylformic acid. However, benzoylformic acid remained unchanged for 120 min under the present oxidation conditions (Run 15). An appreciable amount of benzoic acid was formed in the nitric acid oxidation of the oxime (**5**) and benzoylnitromethane (**4**) even at 26 °C, although no benzoylformic acid was formed (Runs 1 and 9). Since nitrogen dioxide adds easily to unsaturated bonds even at a low temperature,[10,13] the



Scheme 3.



Scheme 4.

formation of benzoic acid may be explicable by assuming the hydrolysis of αα-dinitro-α-nitrosoacetophenone (**11**), which will be formed by the further addition of nitrogen dioxide to the nitrolic acid (**9**) and partly by nitrosation of benzoyldinitromethane (**10**). Since the yield of furazan 2-oxide was increased under a low nitrous acid concentration (Run 7), the above assumption seems reasonable.

The Mechanism of the Oxidation of Acetophenone.—Based on the results presented above, the most probable route to account for the formation of the furazan 2-oxide (**13**), benzoic acid, and benzoylformic acid may be summarised as presented in Scheme 4. The nitrites shown in Scheme 4 probably have only a transient existence and are susceptible to ready hydrolysis.[15] As shown in Table 4, both the oxime (**5**) and benzoylnitromethane (**4**) gave the products in similar ratio irrespective of the solvent. Table 4 indicates the relative reactivity of benzoylnitromethane (**4**) with the oxime (**5**) in the nitric acid oxidation. However, in the oxidation of acetophenone, one should consider which one is formed in the system: benzoylnitromethane (**4**) or the oxime (**5**). The same discussion as in the case of benzoylnitromethane (**4**) applies to the oxidation of acetophenone. The enol form of acetophenone may be more easily attacked by the nitrosonium ion to give the oxime (**5**), than by nitrogen dioxide to form benzoylnitromethane (**4**), because the preferential electrophilic attack by nitrosonium ion was found even in the case of the enol form of benzoylnitromethane (**5**) with the electron-attracting group. The nitroso tautomer of the oxime (**5**) could be oxidised to benzoylnitromethane (**4**), but the oxidation rate to the furazan 2-oxide (**13**) is expected to be faster than that to benzoylnitromethane (**4**) because although the oxidation of the oxime (**5**) essentially completes within 30 min, that of nitrosobenzene requires more than 2 h.[12] In conclusion, we propose that benzoylformaldehyde oxime (**5**), rather than benzoylnitromethane (**4**), is formed in the nitric acid oxidation of acetophenone, and the overall reaction proceeds as summarised in Scheme 4.

Experimental

Materials.—Benzoylformaldehyde oxime and benzoylnitromethane were prepared according to the literature.[16,17]

Kinetic Measurements.—Nitric acid and acetophenone were thermostatted in aqueous organic solvent at 60 °C. The reaction was initiated by addition of aqueous sodium nitrite. Aliquots were taken at appropriate time intervals and the acetophenone was estimated as described below.

The oxidation of benzoylnitromethane and benzoylformaldehyde oxime was carried out similarly to that of acetophenone. In the case of benzoylformaldehyde oxime, the reaction was started by the final addition of the substrate solution. The oxidation rates, except those of acetophenone, were too fast to measure.

Analytical Method.—A mixture of the aliquot portion (5 ml) and water (30 ml) was extracted with 10 ml and then 5 ml of dichloromethane. The extract was washed with saturated sodium hydrogen carbonate. The organic layer was analysed by h.p.l.c. {Zorbax ODS, MeOH–H_2O [8:2(v/v)], 4.6 mm × 25 cm}. The aqueous layer containing the carboxylic acids was acidified with hydrochloric acid and extracted with ether. The ether extract was treated with ethereal diazomethane and analysed by g.l.p.c. (PEG-20M 5% on Chromosorb W AW; 3 mm × 2 m and Silar 10C 10% on Chromosorb W AW; 3 mm × 3 m at 120 °C). G.l.p.c. and h.p.l.c. were run with a Shimadzu GC-4BPF model and a JASCO TRI ROTAR III model.

The nitrous acid content was estimated by the absorbance at 535 nm after its reaction with sulphanilic acid and then with α-naphthylamine. The acidity function was measured by using *o*-nitroaniline as an indicator as described previously.[5] Visible spectra were recorded with a Shimadzu UV-300 spectrophotometer.

Acknowledgements

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