Mechanism of Nitrile-forming Fragmentation Reactions

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Treatment of the 2,4-dinitrophenyl ethers of the *anti*-form of the α-keto-oximes PhCO·C(Ph)=NOH (I) and 2,4,6-$Me_3C_6H_2CO·C(Ph)=NOH$ (II) with the nucleophiles OH⁻, OMe⁻, OPrⁱ⁻ leads to a Beckmann fragmentation with the formation of benzonitrile and the corresponding benzoic or 2,4,6-trimethylbenzoic acids. Similar reactions occur between the benziloxime ether and BuOᵗ⁻ and NH_3, whereas, these nucleophiles substitute the 2,4-dinitrophenyl ring of the ether of (II). The reactions of the 2,4-dinitrophenyl ether of (II) with OH⁻, OMe⁻ and OPrⁱ⁻ follow second-order kinetics ruling out a mechanism involving the rate-determining formation of 2,4,6-trimethylbenzoylium cation. Examination of the oxygen-18 content of recovered 2,4-dinitrophenyl ether of (II) labelled at the carbonyl group after the ether had been subjected to solvolytic conditions, *i.e.* sodium hydroxide in dioxan–water, showed no loss of oxygen-18. The mechanism of the Beckmann fragmentation reaction is discussed in the light of these observations. When the 2,4-dinitrophenyl ethers of (I) and (II) are heated in acetonitrile or benzene, benzonitrile and the 2,4-dinitrophenyl ester of benzoic or 2,4,6-trimethylbenzoic acid are formed. Kinetic measurements suggest that reaction involve an initial Beckmann rearrangement followed by collapse of the resulting nitrilium salt.

THE solvolysis of α-oxo-oxime esters can result in a Beckmann fragmentation [1-4] reaction with the formation of nitriles and carboxylic acid derivatives, *i.e.*

$$RCOC(R) = NX \xrightarrow{H_2O} RCO_2H + RCN + HX.$$

This general class of reactions is of interest mechanistically and as a synthetic path to polyfunctional compounds. Until recently a mechanism involving the rate-determining formation of an acylium cation has been favoured,[3] however, a study [5] of the solvolysis of certain steroid α-oxo-oxime acetates led to the suggestion that a bimolecular solvent-assisted process was involved. We report a study of the mechanism of the Beckmann fragmentation reactions of the 2,4-dinitrophenyl ethers of the α-oxo-oximes (I; X = OH) and (II; X = OH).

The Beckmann fragmentation reaction effectively involves a *trans*-elimination and, therefore, the *anti*-forms of (I; X = OH) and (II; X = OH) were synthesised. The configuration of the oximes was ascertained by observing complex formation with iron(II), copper(II), and cobalt(III) ions, and recently [6] the configuration of the *anti*-form of (I; X = OH) has been confirmed by *X*-ray crystallographic studies.

Both (I; X = OH) and (II; X = OH) formed stable crystalline 2,4-dinitrophenyl ethers, (III) and (IV), on

(I) X = OH
(III) X = 2,4-$(NO_2)_2C_6H_3O$

(II) X = OH
(IV) X = 2,4-$(NO_2)_2C_6H_3O$
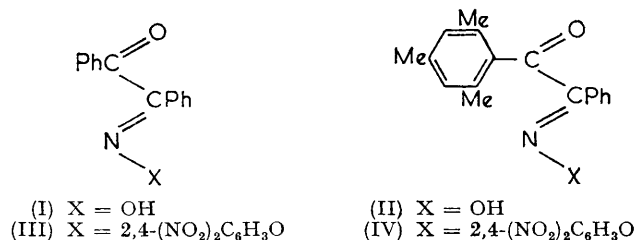
reaction with 2,4-dinitrofluorobenzene. Treatment of (III) with the nucleophiles OH⁻, OMe⁻, OPrⁱ⁻, BuᵗO⁻, and NH_3 resulted in a rapid fragmentation reaction with the formation of benzonitrile and the corresponding benzoic acid derivative. Similarly, reaction of (IV) with OH⁻, OMe⁻, OPrⁱ⁻ anions gave benzonitrile and a

trimethylbenzoic acid, but NH_3 and BuᵗO⁻ anion resulted in substitution of the 2,4-dinitrophenyl ring and formation of the parent α-oxo-oxime (II; X = OH). The course of the latter reaction may be attributed to steric hinderance at the trimethylbenzoyl carbonyl centre, and suggests a bimolecular reaction for the reactions with OH⁻, OMe⁻ and OPrⁱ⁻; the reaction with ammonia, however, cannot be explained on steric grounds.

It was found that, in addition to the fragmentation reactions which occur under solvolytic conditions, both (III) and (IV) fragmented when heated alone in benzene or acetonitrile to form benzonitrile and the 2,4-dinitrophenyl esters of benzoic and trimethylbenzoic acid respectively.

The reaction of (IV) with nucleophiles proceeded at a convenient rate for kinetic measurements and was studied in detail. The rate of reaction was followed by

TABLE 1

Rate of reaction of (IV) with sodium hydroxide in dioxan–water [4 : 1 (v/v)]; all concentrations in moles/l.

[(IV)] × 10⁻⁴	[OH⁻] × 10⁻²	Temp. °c	$k_1 \times 10^4$ (sec.⁻¹)	$k_2 \times 10^{-2}$ (l. mole⁻¹ sec.⁻¹)
1·64	1·20	37·5	1·07	8·96
1·62	1·81	,,	1·58	8·75
1·59	2·40	,,	2·08	8·68
1·61	2·85	,,	2·39	8·70
1·60	3·20	,,	2·58	8·08
1·60	2·40	43·5	3·15	13·12
1·61	3·20	,,	4·12	13·22
1·61	2·40	49·6	5·68	22·70
1·60	3·20	,,	7·32	22·90
1·62	2·40	59·3	12·40	51·80
1·61	3·20	59·3	15·30	49·10

observing spectrophotometrically at 400 mμ, the liberation of 2,4-dinitrophenoxide anion and in some cases by measuring benzonitrile production by using g.l.c.

The rate of reaction of (IV) with hydroxide anion in aqueous dioxan (Table 1), methoxide anion in methanolic

[1] C. A. Grob and P. W. Schiess, *Angew. Chem., Internat. Edn.*, 1967, **6**, 1.
[2] A. Hassner and I. H. Pomerantz, *J. Org. Chem.*, 1962, **27**, 1760.

[3] A. F. Ferris, G. S. Johnson, and F. E. Gould, *J. Org. Chem.*, 1960, **25**, 496.
[4] A. F. Ferris, *J. Org. Chem.*, 1960, **25**, 12.
[5] A. Hassner and W. A. Wentworth, *Chem. Comm.*, 1965, 44.
[6] K. A. Ken, J. M. Robertson, and G. A. Sim, *Chem. Comm.*, 1967, 170.

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TABLE 2

Rate of reaction of (IV) with sodium methoxide in dioxan–methanol; all concentrations in moles/l.

[(IV)] $\times 10^{-4}$	[OMe$^-$] $\times 10^{-3}$	Temp. °C	Solvent composition MeOH (v/v)	$k_1 \times 10^4$ (sec.$^{-1}$)	k_2 (l. mole^{-1} sec.$^{-1}$)
1·80	1·81	37·5	10	47·9	2·66
1·80	2·70	,,	10	60·9	2·25 *
1·80	3·61	,,	10	89·1	2·48
1·70	1·83	,,	15	22·5	1·23
1·70	2·74	,,	15	32·3	1·18
1·70	1·61	,,	20	12·2	0·761
1·60	2·41	,,	20	21·3	0·771 *
1·60	3·22	,,	20	26·5	0·83
1·60	1·61	41·9	20	18·7	1·16
1·60	2·41	,,	20	24·8	1·03
1·60	3·22	,,	20	33·8	1·05
1·60	1·61	47·3	20	23·4	1·45 *
1·60	2·41	,,	20	34·3	1·38
1·60	3·22	,,	20	45·1	1·40
1·60	1·61	53·3	20	39·6	2·46

* Essentially identical rates were obtained by measuring the formation of C_6H_5CN by g.l.c.

dioxan (Table 2), and isopropoxide anion in isopropyl alcohol–dioxan (Table 3) was found to be linearly dependent upon nucleophile concentration, *i.e.*, a bimolecular reaction. Calculation of the entropies and

TABLE 3

Rate of reactions of (IV) with sodium isopropoxide in dioxan–isopropyl alchol [4 : 1 (v/v)]; all concentrations in moles/l.

| [(IV)] $\times 10^{-4}$	[OPr^{i-}] $\times 10^{-3}$	Temp. °C	$k_1 \times 10^3$ (sec.$^{-1}$)	k_2 (l. mole^{-1} sec.$^{-1}$)
1·61	1·60	37·5	1·67	0·104
1·60	2·40	,,	2·36	0·098
1·58	3·20	,,	3·45	0·108
1·60	4·00	,,	4·12	0·103
1·59	4·80	,,	4·85	0·101

enthalpies of activation of the reaction of (IV) with hydroxide and methoxide anions gave the values $\Delta H = 15\cdot9$ kcal./mole^{-1} and $\Delta S = -16\cdot1$ e.u. [for sodium hydroxide in dioxan–water (4 : 1)] and $\Delta H = 13\cdot6$ kcal./mole^{-1} and $\Delta S = -15\cdot5$ e.u. [for sodium methoxide in dioxan–methanol (4 : 1)]. The high negative-entropy values are consistent with, and of the order expected for, those of a bimolecular process.

These observations rule out the possibility of a mechanism for the reaction of (IV) with the nucleophiles OH$^-$, OMe$^-$, and OPr^{i-}, which involves the rate-determining formation of a trimethylbenzoyl cation; such a mechanism cannot be excluded, however, for the corresponding reactions in neutral water, methanol, or isopropyl alcohol.

There are two mechanisms, which need to be considered for the bimolecular reaction. First a process analogous to that which has been well established for the alkaline hydrolysis of carboxylic esters, *i.e.* a $B_{AC}2$ mechanism.

It has generally been assumed that formation of an sp^3 hybridised intermediate of the type depicted would be severely restricted by the presence of the two *ortho*-methyl groups present in the trimethylbenzoyl system

and, therefore, the observation that the bulky nucleophile OPr^{i-} can participate in a bimolecular reaction at a trimethylbenzoyl centre would appear to rule out mechanism (A).
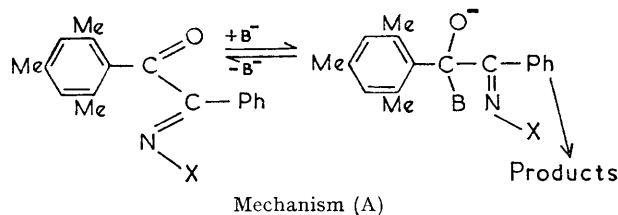
Mechanism (A)

An alternative mechanism, which does not suffer from these limitations, and is fully consistent with the experimental data, is a concerted process resembling in some respects the S_N2-type mechanism. A mechanism of this
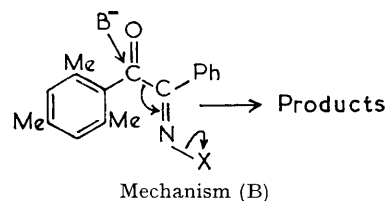
Mechanism (B)

type has been previously suggested [5] for the methanolysis of an α-oxo-oxime acetate.

In order to clarify further the question of the mechanism of the bimolecular fragmentation reaction, the carbonyl group of (IV) was labelled with oxygen-18 (1·400 atom % excess of ^{18}O) by reaction of PhCH$_2$C^{18}OCl with mesitylene in the presence of AlCl$_3$ followed by nitrosation with isopentyl nitrite, and reaction with 2,4-dinitrofluorobenzene. The labelled α-oxo-oxime ether (IV) was treated with sodium hydroxide in dioxan–water [4 : 1 (v/v)] at 37·5°. When approximately 50% reaction had occurred the reaction was terminated by addition of acid. Unchanged (IV) was isolated and the 2,4-dinitrophenyl group was cleaved by reaction with liquid ammonia to give labelled α-oxo-oxime (II). The oxygen-18 content of (II) was determined by Rittenberg and Ponticorvo's method,[7] *i.e.* pyrolysis with mercuric chloride.

In four such experiments the average (maximum deviation 0·014%) oxygen-18 content of the recovered α-oxo-oxime (II) was 0·696 (atom % excess ^{18}O). Blank experiments on (IV), which had not been exposed to solvolytic conditions, gave an average (maximum deviation 0·010%) of 0·701 (atom % excess ^{18}O).

These experiments demonstrate that if mechanism (A) applies then the tetrahedral intermediate depicted dissociates to products more readily than to reactants. The alternative mechanism (B) is fully consistent with the absence of oxygen-18 from unchanged (IV).

Although the experiments strongly suggest mechanism (B) for the bimolecular reactions of the α-oxo-oxime ether (IV), there remains the possibility that mechanism

[7] D. Rittenberg and L. Ponticorvo, *Internat. J. Appl. Radiation Isotopes*, 1956, **1**, 208.

(A) applies for the hydroxide and methoxide anion attack, and that the tetrahedral addition intermediate collapses extremely rapidly to products, because of steric compression in (IV) and in the intermediate. However, it seems unlikely that the bulky nucleophile OPr^{i-} could add to a trimethylbenzolium carbonyl centre.

As mentioned previously the α-oxo-oxime ethers (III) and (IV) fragment when heated alone under nonsolvolytic conditions. The mechanism of these reactions was briefly investigated. The rate of fragmentation was followed by g.l.c. estimation of liberated benzonitrile; the reaction was carried out in acetonitrile and benzene.
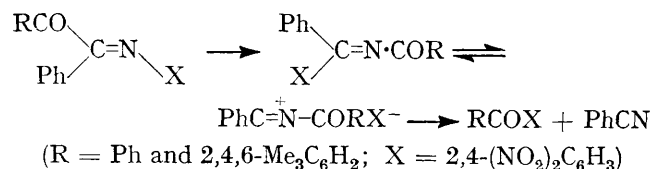
The reactions followed first-order kinetics (Table 4),

TABLE 4

Rate of rearrangement of (III) (0·128 moles/l.) and (IV) (0·115 moles/l.) in acetonitrile and benzene

	Solvent	Temp. °c	$k_1 \times 10^4$ (sec.$^{-1}$)
Reactions of (III)	MeCN	81·5	0·49
	,,	,,	0·51
	,,	,,	0·48
Reactions of (IV)	,,	,,	8·10
	,,	,,	8·00
	,,	75·6	3·88
	,,	69·7	2·48
	,,	63·0	1·19
	PhH	81·5	1·07
	,,	,,	1·00
	,,	,,	1·10

and calculation of the enthalpy and entropy of activation for the fragmentation of (IV) in acetonitrile gave the values $\Delta H = 25\cdot9$ kcal./mole^{-1} and $\Delta S = -3\cdot95$ e.u. The relatively small solvent effect, i.e. $k_{\text{MeCN}}/k_{\text{C}_6\text{H}_6} = 8$, and the observation that (IV) fragmented only 16 times faster than (III) suggests that reaction does not involve the rate-determining formation of acylium cation followed by capture by 2,4-dinitrophenoxide anion. It is tentatively suggested that a Beckmann rearrangement occurs with little charge-separation, followed by rapid reaction of the resultant nitrilium salt with 2,4-dinitro-phenoxide anion:

$$\text{PhC}\overset{+}{=}\text{N–CORX}^- \longrightarrow \text{RCOX} + \text{PhCN}$$

(R = Ph and 2,4,6-Me$_3$C$_6$H$_2$; X = 2,4-(NO$_2$)$_2$C$_6$H$_3$)

EXPERIMENTAL

The mass-spectrometric measurements were carried out on an A.E.I. MS9 spectrometer. Benzonitrile was estimated on a Perkin–Elmer 452 gas chromatograph with a 2 m. column packed with Apiezon on Chromosorb.

Preparation of α-Phenylketo-oxime (II).—A solution of isopentyl nitrite (15·8 g., 0·125 mole) in ether (25 ml.) was added dropwise to a stirred solution of hydrochloric acid (2 ml.) and 2,4,6-trimethyldeoxybenzoin (25 g., 0·11 mole) in ether (100 ml.). When the addition was complete the product was extracted with 5% aqueous sodium hydroxide (3 × 3 ml.) and precipitated by acidification with glacial

acetic acid. Recrystallisation from aqueous ethanol [2 : 3 (v/v)] gave (II) (19·6 g., 70%), m.p. 155° (Found: C, 76·1; H, 6·5; N, 5·0%. C$_{17}$H$_{17}$NO$_2$ requires C, 76·4; H, 6·4; N, 5·3%), ν$_{max.}$ (Nujol and hexachlorobutadiene) 3240s, 2180s, 1645s, 1608w, 1308s, 1215w, 1155w, 1037m, 1003s, 997s, 910w, 861w, 732m, 713s, and 690 cm.$^{-1}$.

Preparation of (III).—2,4-Dinitrofluorobenzene (5·0 g., 0·03 mole) in chloroform (10 ml.) was added to a stirred two-phase solution of α-benzil monoxime (4·50 g., 0·02 mole) and sodium carbonate (4·06 g., 0·04 mole) in water (50 ml.) and chloroform (50 ml.). After 48 hr. the chloroform layer was dried (MgSO$_4$) and then reduced in volume to 10 ml. under reduced pressure. Addition of light petroleum (b.p. 40—60) gave a white crystalline precipitate of (III) (5·5 g., 71%), m.p. 108—108·5° (from chloroform-pentane) (Found: C, 63·9; H, 3·4; H, 11·2%. C$_{20}$H$_{13}$N$_3$O$_6$ requires C, 64·0; H, 3·5; N, 11·2%), ν$_{max.}$ (Nujol and hexachlorobutadiene) 3103w, 1680s, 1610s, 1580m, 1825s, 1380s, 1360s, 1260m, 1237m, 1207m, 1150w, 1130w, 1665w, 940w, 920m, 915m, 872m, 843m, 820w, 807w, 757w, 740m, 720s, 707w, 687m, 652w, and 630m cm.$^{-1}$.

Preparation of (IV).—Similarly, reaction of 2,4-dinitro-fluorobenzene (5·0 g., 0·03 mole) with phenylketo-oxime (5·34 g., 0·02 mole) gave (IV) (6·95 g., 80%), m.p. 137° (from CCl$_4$) (Found: C, 62·9; H, 4·4; N, 10·1%. C$_{23}$H$_{20}$N$_3$O$_6$ requires C, 63·5; H, 4·7; N, 9·9%), ν$_{max.}$ (Nujol and hexachlorobutadiene) 3130w, 2930w, 1703m, 1615s, 1600m, 1540s, 1475s, 1351s, 1320m, 1257w, 1236m, 1216m, 1152w, 1067w, 932m, 920w, 875w, 860w, 845w, 840w, 735m, and 693w cm.$^{-1}$.

The Reaction of (III) *with Nucleophiles.*—(a) *With sodium hydroxide in water–dioxan.* Benzoic acid, 2,4-dinitrophenoyl and benzonitrile were separated by counter-current distribution and identified by comparison (i.r.) with authentic samples.

(b) *With sodium methoxide isopropoxide and t-butoxide in the respective alcohol and dioxan.* Methyl, isopropyl and t-butyl benzoate also benzonitrile were identified and estimated by g.l.c. after extraction of 2,4-dinitrophenol with aqueous alkali.

(c) *With ammonia.* The liquid ammonia was allowed to evaporate off and the products benzamide, 2,4-dinitro-phenol, and benzonitrile separated by counter-current distribution.

The Reactions of (IV) *with Nucleophiles.*—(a) *With sodium hydroxide in water–dioxan.* 2,4,6-Trimethylbenzoic acid, 2,4-dinitrophenol, and benzonitrile were separated by counter-current distribution.

(b) *With sodium methoxide, isopropoxide and t-butoxide in the respective alcohol and dioxan.* Methyl and isopropyl 2,4,6-trimethylbenzoate also benzonitrile were identified and estimated by g.l.c. t-Butyl 2,4-dinitrophenyl ether separated by fractional crystallisation and identified by comparison (i.r.) with an authentic sample.

(c) *With ammonia.* 2,4-Dinitroaniline and (II) were separated by fractional crystallisation from pentane–ethyl acetate.

The Thermal Decomposition of (III).—The oxime ether (III) (1·5 g., 3·9 mmoles) was heated under reflux in aceto-nitrile (25 ml.) for 16 hr. The solvent was removed under reduced pressure and addition of pentane to the oily residue gave a solid, which on recrystallisation from carbon tetra-chloride afforded 2,4-dinitrophenyl benzoate (1·05 g., 70%), m.p. 132° (Found: C, 53·9; H, 2·8; N, 9·6%. Calc. for C$_{13}$H$_8$N$_2$O$_6$: C, 54·2; H, 2·8; N, 9·7%).

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The Thermal Decomposition of (IV).—A similar reaction with (IV) (1·0 g., 2·52 mmoles) in acetonitrile (25 ml.) gave, after recrystallisation from carbon tetrachloride, 2,4-*dinitrophenyl* 2,4,6-*trimethylbenzoate* (0·74 g., 89%), m.p. 166—168° (Found: C, 56·1; H, 4·3; N, 8·2%. $C_{16}H_{14}N_2O_6$ requires C, 56·3; H, 4·3; N, 8·5%), $\nu_{max.}$ (Nujol) 1740s cm.$^{-1}$.

Preparation of Oxygen-18 Labelled (IV).—Water (1·69 atom % excess oxygen-18) (36 ml.) was added to phenyl-acetyl chloride (77 g., 0·5 mole) in dioxan (300 ml.). After 3 days at room temperature the solvent was removed under reduced pressure to afford phenylacetic acid (66 g., 83%), which was treated with phosphorus pentachloride (104 g., 0·5 mole) to give phenyl[^{18}O]acetyl chloride (71 g., 94%). The oxygen-18 of the chloride was shown to be 1·40 atom % excess ^{18}O by Rittenberg and Ponticorvo's method (*i.e.* pyrolysis of the amide in the presence of $HgCl_2$).[7] Labelled phenylacetyl chloride was converted to (IV) by the procedure detailed for the isotopically normal material. Determination of the oxygen-18 content of (IV) by the method detailed below gave a value of 0·701 atom % excess ^{18}O (*i.e.* no loss of ^{18}O occurred during the synthesis of (IV)].

Estimation of Oxygen-18 Content of (IV).—The ether (IV) was treated with liquid ammonia and the products (II) and 2,4-dinitroaniline were separated by crystallisation from pentane–ethyl acetate. The oxygen-18 content of (II) was determined by Rittenberg and Ponticorvo's method.[7]

Kinetic Measurements.—The reaction of (IV) with nucleophiles was studied under pseudo first-order conditions. No deviations were observed from first-order kinetics. The reactions were followed spectrophotometrically on a Unicam SP 800 spectrometer by measuring absorption at 400 mμ (2,4-dinitrophenoxide anion).

The thermal decomposition of (III) and (IV) in aceto-nitrile and benzene was followed by using an ampoule technique; the volatile products, benzonitrile, being estimated by g.l.c. The reactions followed first-order kinetics.