

ANHYDROUS GLYCOLYSIS OF NITRILES

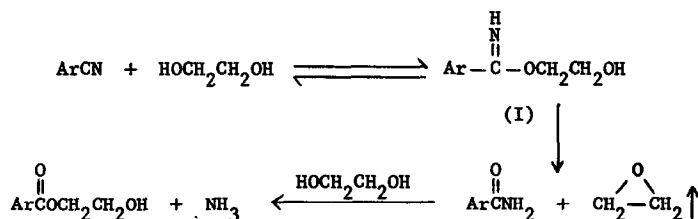
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The alcoholysis of nitriles in refluxing ethylene glycol is a well-known method to prepare β -hydroxyethyl esters (1); however, the mechanism of this reaction is not yet clearly understood. The anhydrous reaction of ethylene glycol with benzonitrile is reported (2) to evolve ethylene oxide, as well as ammonia.



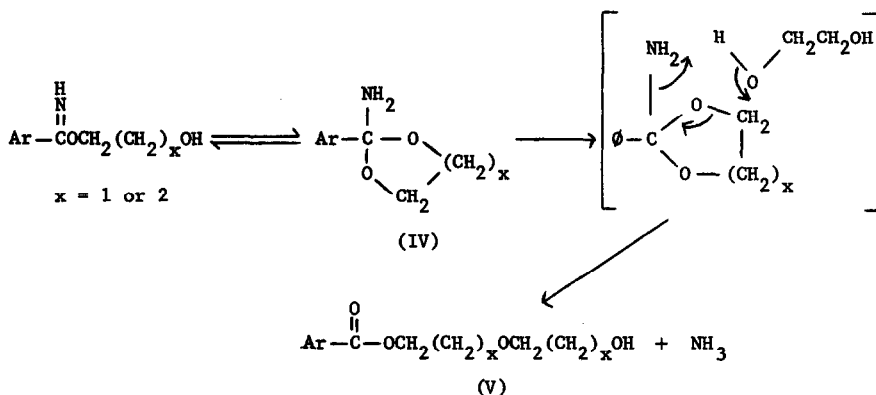
Kinetic studies (4) are consistent with the initial formation of 2-hydroxyethyl benzimide, (I); however, Ikeda et. al. (3,4) propose that (I) reacts with excess ethylene glycol to form orthoesters (II) or (III), rather than to form a benzamide. The anhydrous hydrolysis



reaction of terephthalonitrile gave "scarcely any 2-hydroxyethyl p-cyanobenzoate" (4); addition of water resulting in ester formation.

We have found that the anhydrous reaction of glycols with nitriles evolves ammonia at 130° to 200°C. directly yielding esters. The kinetic^(c) product is a 2-(2-hydroxyethoxy)-ethyl ester that transesterifies in the excess ethylene glycol to form the β -hydroxyethyl ester.^(a)

In view of these new facts, it is proposed that the reactive intermediate is an amide ethylene or propylene acetal (IV). This intermediate is consistent with the lack of reactivity shown by monohydric alcohols which would have evolved ammonia if orthoesters were the intermediates.



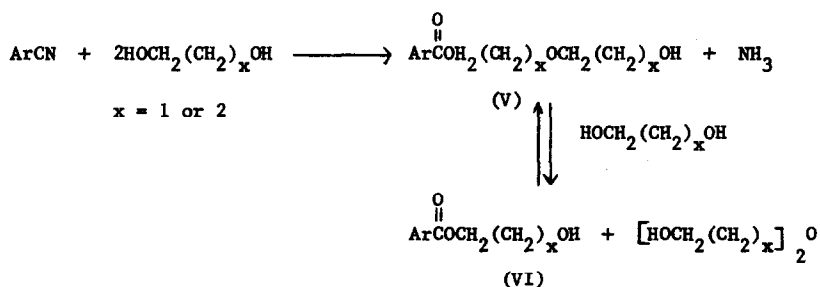
Benzamide ethyleneacetal (IV) was not isolated, but this class of compounds is known to be substantially more reactive than orthoesters and various specific examples have been cited as reactive intermediates in rearrangement reactions (8).

Ethylene glycol transesterification (9) of (V) yields the 2-hydroxyethylester (VI) at a rate considerably slower than the nitrile glycolysis reaction liberated ammonia (4,5). The fact that the rate of diethylene glycol appearance in solution is slower than that of ammonia evolution (Table I) is further evidence against the intermediacy of diethylene glycol formed from ethylene oxide and ethylene glycol, or for a unique ring opening of orthoester (II).

Table I

GLYCOLYSIS OF TEREPHTHALONITRILE (0.195 moles) IN REFLUXING
ANHYDROUS ETHYLENE GLYCOL (2.52 moles) AT 195°C

<u>Time</u> <u>(min.)</u>	<u>Moles NH₃</u> <u>(evolved)</u>	<u>Moles Diethylene</u> <u>Glycol in E.G. Solution</u> ^(b)
3	0.015	0.011
43	0.147	0.029
95	0.188	0.054
161	0.226	0.073
228	0.252	0.094
307	0.276	0.098
580	0.301	0.153
1245	0.325	0.206



This unusual reaction is limited to 1,2 and 1,3 diols. Monohydric alcohols: 1-octanol, 2-methoxyethanol, 2-phenylethanol (2), 1-decanol, and 2-ethoxyethanol (2) produced only trace quantities of ammonia when refluxed with aromatic nitriles. Dihydric alcohols such as diethylene glycol and triethylene glycol were unreactive; whereas, 1,5-pentane diol (2) and 1,6-hexane diol (2) gave esters very slowly. Carefully purified 1,4-butanediol at reflux temperature is unreactive with benzonitrile or terephthalonitrile unless a trace amount of an acidic catalyst or metal salt (5) is added as contrasted to its earlier reported reactivity (2). Addition of zinc acetate (0.2g) to a refluxing solution of terephthalonitrile (0.195 moles) and 1,4-butanediol (2.52 moles) resulted in the evolution of copious amounts of ammonia (0.388 moles) and tetrahydrofuran (0.397 moles) yielding the expected 4-hydroxybutyl ester.

Ethylene oxide conceivably could react rapidly with the ethylene glycol to give diethylene glycol which might selectively alcoholize the amide intermediate to form the kinetically observed product. However, the rate of glycolysis, i.e., ammonia evolution, from the reaction of benzamide in refluxing ethylene glycol is about one-third that of benzonitrile (4). Likewise we have found the rate of ammonia evolution (10) from terephthalamide with ethylene glycol or diethylene glycol to be about one-tenth that of terephthalonitrile glycolysis with ethylene glycol. Mass spectral analysis of the effluent gases detected no ethylene oxide, propylene oxide or their reaction products with ammonia (6).

Infrared analysis of the terephthalonitrile:ethylene glycol reaction solutions showed ester carbonyl functionality at 5.75 μ incipient with ammonia evolution. There was a linear relationship between the increase in the ester carbonyl absorption intensity at 5.75 μ and the mole % of ammonia evolved. Additionally, the characteristic absorption bands of ortho esters similar to (II) and (III) synthesized by McElvain and Starn (7) were completely absent.

We suggest that the amide acetals are also the reactive intermediates in the aqueous glycolysis of nitriles. The distinction in mechanism is in the relative nucleophilicity of water versus glycol in the ring opening steps, necessitating carefully designed procedures to control the addition of water, thereby optimizing the yield of the desired β -hydroxyethyl ester (11).

The high yield synthesis (12) of bis(β -chloroethyl)-terephthalate by heating a solution of ethylene glycol and terephthalonitrile saturated with hydrogen chloride is mechanistically consistent with this hypothesis; the product arises from a selective nucleophilic attack of chloride ion upon the protonated amide ethyleneacetal (V).

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FOOTNOTES

- (a) Compound V separated from VI by TLC on silica gel (6% CH_3OH + 94% CHCl_3); NMR of V ($\text{Ar} = \text{O}$); $-\overset{\text{O}}{\parallel}{\text{C}}-\text{OCH}_2$, $\delta = 4.44$ ppm; $-\text{CH}_2\text{OH}$, $\delta = 3.90$ ppm; $-\text{CH}_2\text{OCH}_2-$, quartet, $\delta = 4.17$ ppm; $J = 5.5$ cps.; colorless low melting wax.
- (b) DEG in EG calculated from VPC data using internal standards.
- (c) TLC was used to monitor Compounds V and VI during reaction.