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THE DETECTION OF HYDROGEN CYANIDE PRESENT AS AN IMPURITY IN N,N-DIMETHYLFORMAMIDE

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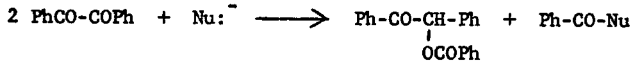
We would like to report the detection of hydrogen cyanide as an impurity in N,N-dimethylformamide (DMF). This information will be of unusual significance to those working with this solvent where the presence of cyanide, if not recognized, might lead to strange behavior of reactants.

Recently, an anomaly such as this was encountered in this laboratory.[1,2] It was discovered that benzil reacts with certain nucleophiles (phenoxide, t-butoxide, and hydroxide) in DMF to form benzoin benzoate (1) and the corresponding benzoylated nucleophile (eq. 1). The reaction occurs within minutes and yields are good. With the exception of hexamethylphosphoramide[3], other aprotic solvents tested were incapable of effecting the reaction.



$$2\ \mathrm{PhCO{-}COPh} + \mathrm{Nu:}^{-} \longrightarrow \underset{\displaystyle \mathrm{OCOPh}}{\mathrm{Ph{-}CO{-}CH{-}Ph}} + \mathrm{Ph{-}CO{-}Nu} \qquad (1)$$

1

Subsequently, a preliminary rate study was begun of the benzil-phenoxide reaction which resulted in the discovery that the reaction rate was second order with respect to benzil and zero order in phenoxide. It became apparent that solvent from different containers (regardless of source) resulted in different reaction rates, although the method of solvent purification was the same in each case, i.e., distillation from calcium hydride. Furthermore, exposure of the distillate to sunlight caused an enhancement of rate.

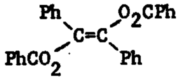
The method of solvent purification finally adopted consisted of refluxing DMF for 4-6 hours in the dark over calcium hydride at ca. 40 mm followed by fractional distillation, whereby a middle cut was collected and stored in a dark bottle away from sunlight. This treatment was sufficient to remove the catalytic impurity since solvent purified in this manner resulted in a negligible rate. A plot of the second order rate constant versus volume percent of "impure" DMF in "purified" DMF or dimethyl sulfoxide (DMSO) was linear demonstrating first order dependence of the reaction rate on the impurity.

An investigation was begun to evaluate likely impurities (*e.g.*, formic acid, dimethylamine, carbon monoxide, carbon dioxide, oxygen, water, formamide, and N-methylformamide) for their catalytic activity. However, all substances tested had a negligible or negative effect on the reaction rate.

Although to our knowledge, *hydrogen cyanide* has not been previously recognized as an impurity in DMF, its presence would account for the apparent reaction between benzil and phenoxide in this solvent (eqs. 2-4). The first step in the sequence, which is generation of cyanide ion, is guaranteed by the presence of base, *e.g.*, phenoxide ion. Cyanide ion, once formed, is able to transform benzil into *trans*-α,α'-stilbenediol dibenzoate (**2**), which in turn reacts with nucleophile to form **1** and benzoylated nucleophile.

$$\text{H-CN} + \text{PhO}^- \rightleftarrows \text{CN}^- + \text{PhOH} \qquad (2)$$

$$2\ \text{PhCO-COPh} + \text{CN}^- \longrightarrow \qquad (3)$$



$$\text{Ph(PhCO}_2\text{)C=C(O}_2\text{CPh)Ph}$$

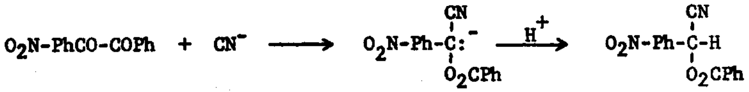
2

$$\mathbf{2} + \text{PhO}^- \longrightarrow \mathbf{1} + \text{Ph-CO}_2\text{-Ph} \qquad (4)$$

Formation of **2** in aprotic solvents (eq. 3) has been well established[4,5] and the reaction of **2** with phenoxide (eq. 4) has been shown in this work to proceed very rapidly to **1** and phenyl benzoate in near quantitative yields.

To support the argument for hydrogen cyanide in DMF, a study was made of the effect of known cyanide on the rate of the benzil-phenoxide reaction in "purified" DMF and DMF/DMSO mixtures. A plot of the second order rate constant versus cyanide concentration was linear. Although these data support the results described above, *i.e.*, first order dependence of the reaction rate on impurity, it does not constitute unequivocal proof of the presence of hydrogen cyanide as an impurity in DMF.

In another study[6] it was observed that 4-nitrobenzil reacts with cyanide ion in DMF or DMSO (eq. 5) to form 4-nitromandelonitrile benzoate (**4**). The reaction has proven useful as a method for actually trapping cyanide, thus demonstrating its presence in "impure" DMF samples. In a typical procedure, 2.0 mmole of 4-nitrobenzil was dissolved in 800 ml of "impure" DMF. Sodium hydride was added for the purpose of generating cyanide ion. The system immediately became deep violet in color owing to the formation of **3**.[7] The solution was poured into cold aqueous acid and extracted with ether. The ether residue was placed on a column of silicic acid and eluted with 3-10% ether-petroleum ether to produce unreacted 4-nitrobenzil and a small quantity of **4** (m.p. 113-115°). Structure elucidation was achieved by mixture melting point and comparison of spectral data with that of an authentic sample.[6]



$$O_2N\text{-}PhCO\text{-}COPh + CN^- \longrightarrow O_2N\text{-}Ph\text{-}\overset{CN}{\underset{O_2CPh}{C}}:^- \xrightarrow{H^+} O_2N\text{-}Ph\text{-}\overset{CN}{\underset{O_2CPh}{C}}\text{-}H \qquad (5)$$

3 **4**

Estimation of hydrogen cyanide concentration has been accomplished by relating the rate of the benzil-phenoxide reaction in "impure" DMF to that in "purified" DMF and DMF/DMSO mixtures where the concentration of cyanide is known. Using this method, concentrations of hydrogen cyanide have ranged from 10^{-5} to 10^{-3} molar in "impure" DMF samples.

Alternate methods for estimating hydrogen cyanide concentration are now under consideration. One especially attractive and relatively simple procedure is the measurement of the concentration of highly colored **3** by u.v. spectroscopy.

REFERENCES

1. J. C. Trisler, J. D. Cheng and B. F. Freasier, J. Org. Chem., **35**, 2693 (1970).
2. For an additional example of the "cyanide effect" in DMF, see: G. R. Newkome and J. M. Robinson (accompanying paper).
3. Unpublished results obtained with J. D. Cheng. The reaction was less effective in that lower yields were obtained.

4. J. C. Trisler and J. L. Frye, *J. Org. Chem.*, *30*, 306 (1965).

5. J. P. Kuebrich and R. L. Schowen, *J. Am. Chem. Soc.*, *93*, 1220 (1971).

6. Results obtained with J. E. Wilson and W. R. Reardon to be published elsewhere.

7. Anion **3**, λ_{max} 540 nm, can also be generated either from the reaction of 4-nitrobenzil with known cyanide or by the reaction of **4** with base in aprotic solvent.