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EXCHANGE BETWEEN LABELLED CYANIDE AND THE NITRILE FUNCTION OF ACETONITRILE

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ABSTRACT: Labelled potassium cyanide, dissolved in acetonitrile with the aid of a crown ether, exchanges with the nitrile function of the solvent resulting in labelled acetonitrile.

In recent years, there has been a renewed interest in the use of carbon-11 as a radioisotopic tracer. Its short half-life and emission characteristics offer certain advantages over labelling with carbon-14, particularly in biological systems. The most commonly used carbon-11 precursors for the synthesis of compounds labelled with carbon-11 are ^{11}CO, $^{11}CO_2$ and $H^{11}CN$ (or $Na^{11}CN$)[1]. The latter is ordinarily used in the synthesis of ^{11}C-labelled nitriles and amines, some of which are biologically active.

Cyanide salts may be solubilized in organic solvents with the aid of crown ethers to avoid time consuming extraction steps in the synthesis of these labelled nitriles and amines. This is important when noting the 20.4 min half-life of carbon-11. Cook et al.[2] obtained a 94% yield of benzyl cyanide from benzyl chloride in 0.4 hours using potassium cyanide in acetonitrile with 18-crown-6. Similar results were reported by Zubrick et al[3]. When we repeated this reaction with ^{14}C-potassium cyanide, we experienced a significant loss of total radioactivity after extraction into chloroform and subsequent evaporation to remove the solvent acetonitrile.

We wish to report here the observation of exchange between labelled cyanide and the nitrile function of actonitrile. This exchange was apparently responsible for the loss of radioactivity in the ^{14}C-benzyl cyanide reaction. To gain evidence that exchange was occurring, the following reaction was performed: One gram of 18-crown-6 was dissolved in 4 ml of acetonitrile as well as enough 90% enriched $K^{13}CN$ (~ 20 mg) to saturate the solution. This was refluxed at 90° for 25 min. after which time the solvent was distilled and collected. The distillate was subjected to NMR and mass spectral analysis with the following results:

(1) ^{1}H-NMR. An increase in the intensities of the ^{13}C-satellites (of the proton signals) was observed as seen in Table 1.

Table 1 Proton - NMR data comparing signal intensities due to ^{13}C-satellites.

	Sum of relative intensities
Product	15
Acetonitrile	8

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(2) ^{13}C-NMR. The signal due to the ^{13}C-nitrile carbon was enhanced with respect to unreacted acetonitrile (see Table 2).

Table 2 ^{13}C-NMR data comparing signal intensities arising from nitrile carbon.

	Relative signal intensity for $CH_3\text{-}^{13}C{\equiv}N$ ($^{13}CH_3\text{-} = 100$)	$^{13}CH_3CN/CH_3{}^{13}CN$
Product	26	3.85
Acetonitrile	22	4.55

(3) Mass Spectrum. The M+1/M ratio (i.e., m/e = 42/41 rose from 0.031 for unreacted acetonitrile to 0.076 for the distillate.

(4) When the reaction was repeated with K^{14}CN (1.5 μCi), over 48% of the radioactivity was recovered in the distillate.

The NMR and mass spectral data shows an enrichment of the nitrile carbon of acetonitrile with carbon-13. Furthermore, the experiment with K^{14}CN confirmed that exchange was indeed occurring in the attempted synthesis of ^{14}C-benzyl cyanide.

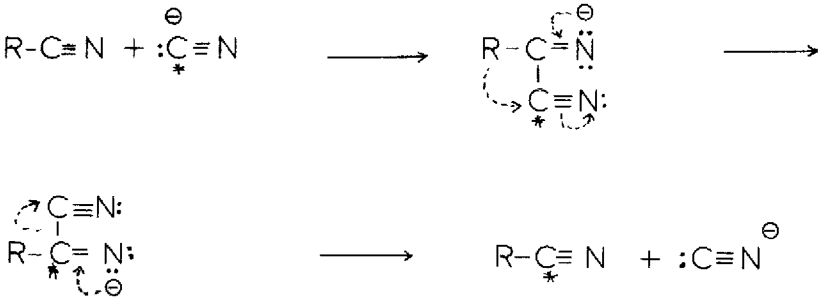
This exchange is of no consequence when non-labelled cyanide is involved. However, when ^{11}C-cyanide is employed, any degree of exchange would take on great significance since the molar quantities of cyanide are minute with respect to the quantity of solvent. The exchange would result in the formation of ^{11}C-acetonitrile causing a decreased radiochemical yield and a radiochemically impure product, since the desired nitrile would not be the only radioactive species present.

Although the cyanide anion is a good nucleophile, the cyano function is a poor leaving group in the S_N2 sense. Nucleophiles such as hydroxide, alkoxides, amines and sodamide are known to attach the electrophilic carbon atom resulting in additions to the $C\equiv N$ bond rather than in S_N2 displacement of the cyano group[4]. A rare example of an apparent "displacement" of a cyano function involves the reaction with a Grignard reagent.

$$R\text{-}C\equiv N + R'MgX \longrightarrow R\text{-}R' + CN\text{-}Mg\text{-}X$$

That such a reaction is not a S_N2 displacement but an internal dissociation of the cyano group was proven by Yoshimura <u>et</u> <u>al</u>[5].

A multistep mechanism more likely than S_N2 displacement for the observed exchange may be represented by the following scheme.



Thus the attack of the cyanide at the electrophilic carbon is followed by a rearrangement analogous to the benzilic acid rearrangement[6]. A loss of the cyanide ion, reminiscent of the benzoin condensation[6], completes the exchange reaction. Such a mechanism predicts the retention of configuration in R while S_N2 displacement predicts inversion. Work is now in progress to varify the course of the reaction.

Although acetonitrile appears to be the best solvent for dissolving inorganic cyanide (utilizing crown ethers), we have found THF to be more suitable for reactions involving labelled cyanide. The solubility is not as great in THF, but there is no exchange reaction occurring which might interfere with the formation of the desired product. Also, the labelled nitrile can be conveniently reduced in THF making a one-pot synthesis of labelled amines possible. This point takes on added significance when it is considered that many drugs as well as physiologically endogenous compounds are amines. Thus, the exchange reaction precludes the use of acetonitrile as a solvent for reactions involving labelled cyanide.

REFERENCES

1. A.P. Wolf and C.S. Redvanly, Int. J. Appl. Rad. Isotopes, 28, 29-48 (1977).
2. F.L. Cook, C.W. Bowers, and C.L. Liotta, J. Org. Chem., 39, 3416-3418 (1974).
3. J.W. Zubrick, B.I. Dunbar, and H.D. Durst, Tetrahedron Lett., 71-74 (1975).
4. J. Yoshimura, Y. Ohgo and T. Sato, Bull. Chem. Soc. Japan, 38, 1809 (1965).
5. "The Chemistry of the Cyano Group", Z. Rapoport, Ed., Chapter 6, Interscience Publishers, N.Y. (1970).
6. J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structures", McGraw-Hill, N.Y. (1968) pp. 803 and 714.

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