PRODUCTION OF CARRIER-FREE $H^{11}CN$ FOR MEDICAL USE AND RADIOPHARMACEUTICAL SYNTHESES. IX.

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A system for the routine production of carrier-free, high-activity $H^{11}CN$ in an on-line process in the effluent stream from a cyclotron gas target is described. The method is highly reproducible and trouble free, and the yields from a given target and synthesis system are entirely predictable. The material is available in the gas phase or in basic solution within 10–12 min after the end of the irradiation. With a current of 30 μA of focused 25-MeV protons impinging on the target, 2 Ci of carrier-free $H^{11}CN$ are produced with the present system in a 45-min irradiation. The material has been used in the preparation of carrier-free ^{11}C-dopamine and ^{11}C-norepinephrine for animal studies, and some investigation has been made of its possible use for blood labeling.

Cyanide labeled with ^{11}C is a moiety of potential utility as great as carbon dioxide in the synthesis of radiopharmaceuticals. Carbon-11-hydrogen cyanide may have direct medical use in such areas as blood volume measurements. Several papers have appeared recently detailing some possible synthetic routes to this compound (*1*), as well as the direct production in a cyclotron target by recoil processes (*2,3*). However, all synthetic routes are tedious and time-consuming, and they all result in products containing various amounts of inactive carrier. The recoil process currently being used in several laboratories (*2*) utilizes less than 50% of the ^{11}C produced, even under optimum conditions. It requires the heating of the target to about 250°C, and it gives rather erratic results in our hands and in other laboratories (*4*).

We have developed a simple, reliable, routine, on-line method for the preparation of this material carrier free, based on the production of $^{11}CH_4$ directly (by radiolysis of the primary products) in a cyclotron target. It is then quantitatively converted to $H^{11}CN$ in the presence of ammonia over platinum wire held at 1,000°C in an on-line process. The target gas is 95% N_2 + 5% H_2 (oxygen-free) irradiated with 25-MeV protons in a 28-cm-long water-cooled target at a pressure of 11 atm. The incident protons are degraded to 18 MeV by the 60-mil aluminum front window and are attenuated to 4 MeV in the target gas (threshold for the $^{14}N(p,\alpha)^{11}C$ reaction). This range of proton energy covers the entire region of maximum cross section for this reaction (*5*). The ammonia required for the synthesis of the $H^{11}CN$ is also produced by radiolysis of the target gas in the target in a quantity sufficient to obviate the necessity for addition of NH_3 to the gas stream. The G-value for ammonia production has been found to be in the range of 0.2–2. At a beam current of 20 μA and with an assumed G-value of 1, a 100-sec irradiation would produce 3 m*M* of NH_3 most of which is scavenged by P_2O_5 after the platinum furnace.

The production of HCN by pyrolysis of hydrocarbons in the presence of ammonia has been used at least since the late 1800's (*6,7*), and many papers on the general subject have been published in the intervening years. A recent paper on the synthesis of $H^{14}CN$ from $Ba^{14}CO_3$ via $^{14}CH_4$ (*8*) impelled us to reinvestigate this process for the production of $H^{11}CN$, particularly since a target system capable of yielding *over 95% of the ^{11}C produced* as $^{11}CH_4$ was readily available (*9*). Since the conversion of methane to cyanide has been found to be virtually quantitative in this system, the result is the use of over 95% of the ^{11}C produced during bombardment.

The target gas is furnished as a pre-mixed tank (Matheson) and is fed into the target at a pressure

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of 150 psi (total pressure 11 atm). The effluent gas from the target is brought into a laboratory adjacent to the cyclotron vault by ⅛-in. copper tubing passing through the shielding wall. The flow rate is 250 cc/min. The gas passes over a lithium hydroxide absorber to remove any $^{11}CO_2$ which may be present (less than 2% of the total in all cases), then through a vent stopcock into a tube containing 15 gm of 8-mil platinum wire wound to fill an 8-cm path in a 1-cm o.d. quartz tube. This is held at 1,000°C during production. The gas then passes through an 8-cm path of granular P_2O_5 to remove some of the ammonia present which came from radiolysis in the target. It is then trapped in a glass radiator trap held at liquid nitrogen temperature. The remaining gas is passed through a ball-type flow meter before escaping. At the end of an irradiation, the gas is allowed to flow for 8 min to flush most of the active gas out of the target itself. It is allowed to vent before the platinum furnace, and the trap is evacuated by a small vacuum line which follows the trap. After 2 min of pumping, the active gas is distilled through the vacuum line into the desired synthesis vessel by warming the trap electrically and cooling the vessel with liquid nitrogen. The carrier-free material can be absorbed in the vessel by a small amount of base (at least 0.05 *N*). If carrier is to be used, a solution of NaCN without added base can also be used for the absorption of the material. In either case, some NH_3 is still present in the material, and it can be removed efficiently if necessary by pumping the solution to dryness after the $H^{11}CN$ has been absorbed. Little activity is lost in this way, and if the absorbing solution has a volume of 100λ, the process takes roughly 2 min. Therefore, the material can be present in a synthesis vessel ready for use within 12 min after the end of bombardment. Alternatively, the $H^{11}CN$ can be trapped directly in either basic or cyanide carrier solution by bubbling the gas through the solution during the run. Because of the high flow rate, however, a minimum of about 5 ml of solution is required in this case, and appreciable ammonia is then present in the final solution.

Among other aspects of this process which are still under study is the possible removal of the excess NH_3 by chemical means in the vacuum system. The minimum hydrogen concentration necessary in the target gas to produce a high yield of methane is still under study, but it is worthy to note that a 1% concentration of H_2 gives less than half the yield of $H^{11}CN$ obtained with the present 5% concentration.

The yields of $H^{11}CN$ on a given target and under standard conditions is completely reproducible and predictable. Under our conditions, with a highly focused proton beam on the front window of the target, the *saturation* yield (in Ci) of $H^{11}CN$ is 0.08 times the proton current in μA. Thus, for a 40-min irradiation, the actual yield of $H^{11}CN$ is 75% of the calculated saturation value. This relationship has been found to hold for irradiations of various lengths, including runs to 95% of saturation (90 min). As an example, a 40-min irradiation at 30 μA produces 1.8 Ci of $H^{11}CN$ as of end of bombardment.

It might also be pointed out that with cyclotrons not capable of accelerating protons to the necessary energies for this system, it would be possible to perform a similar on-line synthesis by incorporating a reduction system such as that described by Banfi, et al (*8*) into the effluent stream of any cyclotron capable of producing $^{11}CO_2$ by one of the systems available for that purpose and thus producing the necessary $^{11}CH_4$ indirectly.

This material has been used to produce ^{11}C-dopamine for use in animal studies by a process similar to that previously published (*10*) but scaled down from the previous level by approximately a factor of 100. In this way, ^{11}C-dopamine with a specific activity of roughly 40 mCi/mg (at the time of delivery) was produced. It has also been used for the preparation of carrier-free ^{11}C-dopamine and carrier-free ^{11}C-norepinephrine in amounts of more than 30 mCi at delivery (*11*). If the linearity of yield versus current-on-target holds up to 100 μA, it should be possible to produce 6–10 Ci of $H^{11}CN$/hr with most medical cyclotrons in current use. Higher proton energies would not be particularly helpful because the cross section for the desired reaction is quite low above about 18 MeV and because other undesirable radioactive nuclides (e.g., ^{7}Be) begin to be produced.

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