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Philip B. Shevlin, Alfred P. Wolf
Chemistry Department, Brookhaven National Laboratory[14]
Upton, New York 11973

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Labeling with Iodine-123. The Reactivity of Iodine-123 Formed by the Decay of Xenon-123[1]

Sir:

Sodd, *et al.*,[2,3] have recently described a "generator" system where 14-hr half-life iodine-123 is prepared as carrier-free iodide ion by the decay of 2-hr half-life xenon-123. The xenon-123 decay occurs in part by electron capture and in part by positron emission.[4] The recoil energy imparted to the iodine may be sufficient for the iodine species formed to react with surrounding molecules. This study was carried out to investigate the reactivity of this generator-produced iodine and to compare this reactivity with that of the iodine species produced directly by nuclear recoil (*i.e.*, ^{128}I formed by the ^{127}I(n,γ)^{128}I reaction) and β^--produced iodine formed in uranium fission.

Natural tellurium was bombarded by the 25-MeV helium-3 beam of the Washington University 54-in. cyclotron and the xenon-123, formed by the ^{122}Te(^{3}He, 2n)^{123}Xe reaction, was swept out of the bombardment chamber in a stream of helium gas and collected in a radiator trap cooled to liquid nitrogen temperature. The xenon was then transferred into various reaction vessels with the trap cooled to $-80°$ to prevent distillation of iodine-123 already formed. No carrier xenon was added and each reaction vessel contained $<10^8$ atoms of xenon.

In this study the xenon was mixed with gaseous methane, benzene frozen at 77°K, and serum albumin at 77°K. Two of these compounds were chosen to compare the iodine reactivity with the activity of recoil iodine produced directly by a nuclear reaction[5-7] while the third compound (serum albumin) was chosen to investigate whether the active iodine would label a compound of biological interest.[8]

In the studies with methane the two gases were mixed in a 100-cc vessel at 760 mm pressure and the xenon was allowed to decay for 6–12 hr. A mixture of methyl iodide and dilute sodium thiosulfate was then added, the vessel shaken, and the mixture removed; the organic and aqueous layers were separated. It was found that 80 ± 9% (average of three experiments) of the activity[9] remained in the organic phase. The integrity of the label was verified by forming pyridinium methiodide, where all the activity was found in the recrystallized salt. In nuclear recoil studies[6] iodine vapor was mixed with the methane to produce the radioiodine and also to scavenge thermal iodine atoms. When $\simeq$0.1 mm of iodine vapor was added to the xenon–methane mixture the organic yield dropped to 48 ± 5%.

In the studies performed with benzene, xenon and benzene were frozen together at 77°K and kept at this temperature for 6–12 hr before the aqueous and organic fractions were separated. In this case 54 ± 5% (average of three experiments) of the activity was organically bound.

A 0.1-g sample of recrystallized serum albumin was placed in an ampoule, the bottom of which was immersed in liquid nitrogen, and the xenon was frozen into the ampoule. The whole ampoule was then immersed in liquid nitrogen for 6–12 hr. After warming the ampoule, the albumin was dissolved in saline solution and the protein precipitated with trichloroacetic acid; it was found that 80 ± 10% of the iodine-123 activity was precipitated with the protein, and was therefore organically bound.

It appears from these studies that the iodine-123 species formed by the decay of xenon-123 are active and, with methane and benzene, have a reactivity similar to that of iodine atoms produced by nuclear recoil. The organic yield observed in the reaction with methane is much higher than that observed in the recoil case[6] (54%); however, when the recoil studies were duplicated by adding small amounts of iodine scavenger to the reaction vessels the yield dropped. As all single displacement or abstraction reactions of thermal iodine atoms or ions with methane are endothermic,[6] this drop in organic yield upon addition of iodine cannot be explained by the iodine scavenging thermal iodine atoms. The drop in yield can only be explained if the scavenger is competing for an excited species.

In the solid state, where scavengers will have less effect due to trapping of the active species in the matrix, the organic yield observed with benzene (54%) is very similar to that observed in the nuclear recoil case (59%).[7] The similarity between the reactivity of the generator-produced species and iodine formed by nuclear recoil is in contrast to the reactivity of β^--produced iodine, where the reactivity was 0.5–0.75 that of iodine formed directly by nuclear recoil.[10,11] This difference can be explained by the fact that the kinetic energy spectrum of species formed by β^- decay contains a larger fraction with low kinetic energy than does the spectrum from β^+ decay. It is therefore to be expected that the generator-produced iodine, with a maximum kinetic energy $\simeq$15 eV and with fewer low energy species, will resemble iodine produced by nuclear recoil more than will iodine produced by β^- decay.

The iodine-123 formed by the decay of xenon-123 is an active species which can be formed with a much lower radiation dose to the sample than can iodine formed

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(1) This work was supported by Public Health Service Grant No. GM14889-06.

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(9) The samples were counted in a well-type scintillation counter attached to a 400-channel analyzer. The ^{123}I activity was determined by measuring the area under the γ peak at 159 keV. This method was used to distinguish the ^{123}I activity from any ^{125}Xe, ^{124}I, and ^{125}I formed. If enriched ^{122}Te had been used as the target these impurities would be minimal (ref 2 and 3).

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directly by nuclear recoil. To produce the iodine-123, it is not necessary for carrier iodine to be present to produce the species; only the small amount of xenon-123 needs to be added. Studies are currently being undertaken to investigate the charge and excitation of the labeling species.

It is also seen that this reactive iodine species will label compounds of biological interest under carrier-free conditions. With enriched tellurium-122 as the target material, it is anticipated that millicurie quantities of labeled compounds can be prepared,[12] using the generator-produced species as the iodinating agent.

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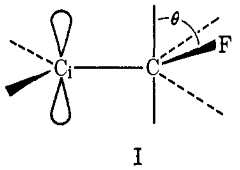
[12] Sodd (ref 3) estimates ^{123}I yields of $\simeq$100 μCi/μA hr; therefore, with a 5-μA beam irradiating to saturation in xenon-123 it should be possible to prepare $\simeq$2 mCi of ^{123}I.

Michael J. Welch
The Mallinckrodt Institute of Radiology
Washington University School of Medicine
St. Louis, Missouri 63110
Received October 6, 1969

The Angular Dependence of β-Fluorine Coupling Constants[1]

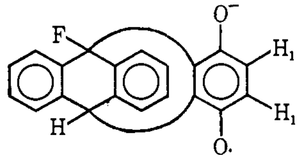
Sir:

Several quite different proposals have been advanced concerning the origin and the angular dependence of the epr coupling constants of β-fluorine nuclei in free radicals. Strom and Bluhm[2] suggested that the coupling constant would be greatest when θ is 90° (I) because the interaction[3] between the p orbital centered on the carbon atom and the nonbonding p orbitals of the fluorine atom would be maximum in this conformation. In contrast, the results of an unrestricted SCF calculation in the INDO approximation indicate that the constant should be virtually zero when θ is 90°.[4] Gerlock and Janzen[5] suggest, on the other hand, that the minimum coupling might occur between 0 and 90°.

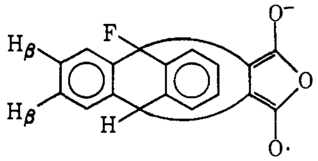


I

We have examined the rigid molecules II and III in which the β-fluorine nucleus is constrained to the nodal plane of the π electron system, θ = 90°, to assess the magnitude of the coupling constant for a fixed conformation.[6] The spectroscopic observations are summarized under the structures.[9] The assignments for II were verified by the examination of the deuterium derivative (H_1 = D).



II, $a_H = 2.6, 2.1$ G (2H), H_1
$a_F = 0.85$ G



III, $a_H = 0.13$ G (4H), H_β
$a_F = 1.26$ G

The results for the semiquinone and the semifuraquinone both indicate that the ^{19}F nucleus exhibits an important coupling when constrained to the nodal plane. For comparison, a_F for 2-trifluoromethylsemiquinone is only about 3-fold greater, 2.7 G. The a_F values for II and III are consistent with the greater electron density at C_2 of the semifuraquinone; however, the difference between these constants is smaller than expected on the basis of hydrogen atom couplings.

Prior work prompted the conclusion that hyperconjugation between the p orbital on C_i and the carbon–fluorine σ bond was not principally responsible for the coupling.[7] The new results indicate, in addition, that a simple $\cos^2 \theta$ relationship is unsuitable for the description of the angular dependence. The finding that a_F is large for II and III together with the knowledge that the constants for such nuclei are highly anisotropic strongly infer that the nonbonding p electrons of the fluorine atom play an important role in the coupling mechanism.[11] Two quite different mechanisms are compatible with these data. On the one hand, an interaction between the p orbitals of fluorine and the π-electron density at C_2 would explain the results. The angular dependence predicted for such an interaction (based on the magnitude of the overlap integral[12] between the p orbital on C_i and the nonbonding p orbitals of the fluorine atom) is shown in Figure 1. This relationship predicts that a_F for a trifluoromethyl group in free rotation should be about 2-fold greater than a_F for a fluorine atom constrained to the nodal plane. The available results, a_{CF_3} = 2.77 G and a_F = 0.85 G, for the semiquinones suggest that the ratio is about 3. The discrepancy between these values is not excessive. Thus, the preliminary findings are consistent with the view that π–p interactions between the aromatic π system and the nonbonding p orbitals on the β-fluorine atom are important in magnetic resonance.[13] On the other hand, the spin density observed for the fluorine nucleus in the nodal plane may result from a direct interaction between the oxygen and fluorine atoms of II and III.[14] Further work will be necessary to assess the importance of this interaction at the internuclear

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[1] This research was supported by the National Science Foundation under Grant No. GP-7448.

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