Synthesis and NMR Characterization of Tri-n-Butyltin Tritide

Devendra K. Jaiswal,[a] Hendrik Andres,*[b] Hiromi Morimoto[a] and Philip G. Williams[a]

[a] *National Tritium Labeling Facility and Structural Biology Division, Lawrence Berkeley Laboratory 75-123, University of California, Berkeley, CA 94720, USA*

[b] *Sandoz Pharma Ltd., Chemical Research and Development, Basel CH-4002, Switzerland*

Tri-n-butyltin tritide, a potentially versatile tritiation reagent, is synthesized at maximum specific radioactivity and characterized by ^{1}H, ^{3}H and ^{119}Sn NMR techniques.

We have treated Li–^{3}H synthesized from carrier-free tritium gas ($^{3}H_2$)[1] with tri-n-butyltin chloride ($Bu^{n}_{3}Sn$–Cl) to produce no-carrier-added tri-n-butyl tin tritide ($Bu^{n}_{3}Sn$–^{3}H, *ca.* 1064 GBq mmol^{-1}). We have characterized the tritiation reagent thus produced by ^{1}H, ^{3}H and ^{119}Sn NMR techniques.†

Organotin hydrides such as tri-n-butyltin hydride (TBTH) are capable, versatile and stable reagents,[2] which are easily prepared. In tritium labelling applications TBTH could be used in a number of obvious ways: (*i*) dehalogenation reactions,[2,3] (*ii*) transition metal catalysed conversion of acyl chlorides to the corresponding aldehydes,[4a] (*iii*) free radical cyclization reactions,[4b] (*iv*) rearrangement reactions such as the production of deoxy sugars from pyranosyl halides[4c] and (*v*) replacement of an OH group with hydrogen,[4d] *e.g.* the conversion of ribonucleosides to 2′-deoxynucleosides.[4e] These and other common applications, especially if achievable in the presence of sensitive functional groups, would vastly increase the tools available to tritiation chemists.

Although routes to labelled TBTH are well-established[2] and deuteriated TBTH is commercially available, there are only two reports on the use of tritiated TBTH.[3a,5] The work by Parnes and Pease[3a] produced tritiated TBTH by two methods; $NaB^{3}H_4$ reduction of $Bu^{n}_{3}Sn$–Cl, and hydrolysis of $Bu^{n}_{3}Sn$–Li with highly tritiated water. Borohydride reduction was the preferred procedure and gave eventual products in good yield (60%), but of mild specific activity (S.A., 2.64 GBq mmol^{-1}). Recently, $NaB^{3}H_4$ reduction was used to produce tritiated TBTH and gave a labelled prostaglandin product of high S.A. (510 GBq mmol^{-1}, *i.e. ca.* 50% of the theoretical maximum).[5] Obviously, the S.A. of the final TBTH reagent is controlled by the tritium content of the $NaB^{3}H_4$, which unfortunately is not currently available carrier-free (usually 50–75% of theoretical S.A.). When carrier-free $^{3}H_2$ is used in the synthesis of $^{3}H_2O$, the hydrolysis procedure[3a] should yield high specific activity products, but the product had a S.A. of 223.5 GBq mmol^{-1} (*ca.* 21% of theory) and the isolation procedure was difficult.[6] Our experience with synthesizing small quantities of highly tritiated water suggests that it is difficult to obtain tritium abundance greater than 70–80%.[7] Hence, the synthesis of maximally tritiated TBTH appears difficult using published procedures.

For these reasons we decided to attempt the generation of $Bu^{n}_{3}Sn$–^{3}H from the reaction of $LiAl^{3}H_4$ with $Bu^{n}_{3}Sn$–Cl, since we could produce fully tritiated $LiAl^{3}H_4$.[1] In early studies it became clear that freshly prepared Li–^{3}H was capable of reducing $Bu^{n}_{3}Sn$–Cl, and we pursued this simpler route with a view to characterizing the product by NMR spectroscopy. After preliminary experiments with ^{2}H, and study by ^{1}H, ^{2}H and ^{119}Sn NMR methods, fully tritiated $Bu^{n}_{3}Sn$–^{3}H was synthesized in the following manner: an evacuated 10 ml side-arm flask was charged with *ca.* 80 kPa of $^{3}H_2$, a solution of $Bu^{n}Li$ in hexanes was injected (1.2 mol dm^{-3}, 166 μl, 0.2 mmol), and the solution was stirred rapidly. Tetramethylethylenediamine (TMEDA, 34 μl, 0.22 mmol) was injected, and a fine white precipitate immediately started to form (Li–^{3}H). After 20 min‡ the excess tritium gas

† A preliminary report was presented at the Fourth International Symposium on the Synthesis and Applications of Isotopically Labelled Compounds, Toronto, Ontario, Canada, September 3, 1991.

‡ Another option is to add a catalytic quantity (10 mol%) of triethylborane after the formation of the lithium hydride, and then proceed with the addition of the tri-n-butyltin chloride solution. We have used both procedures, and the NMR spectra presented in this work are from samples where catalytic triethylborane was not employed.

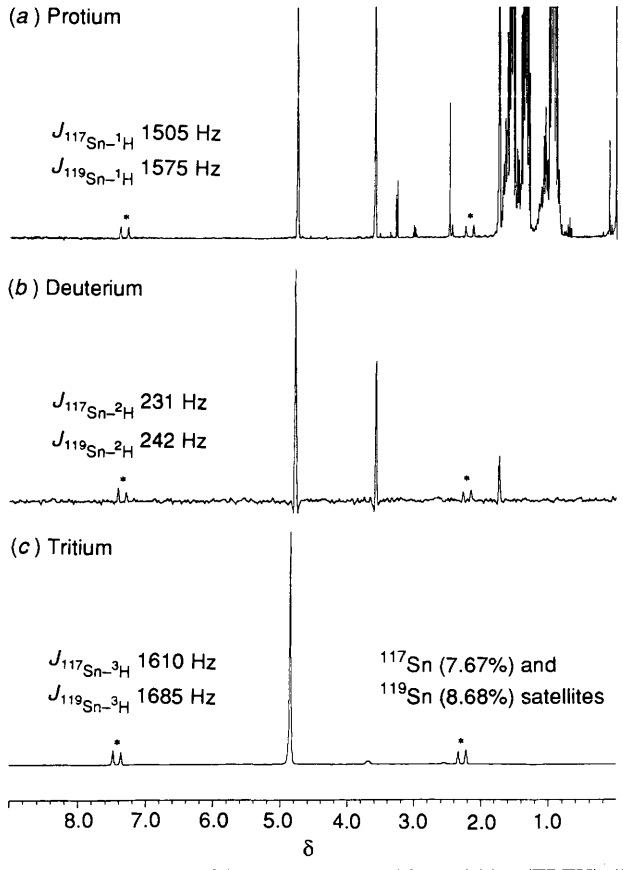

Fig. 1 NMR spectra of isotopic tri-n-butyltin hydrides (TBTH) (δ 9.0–0.0); (*a*) 300 MHz ^{1}H NMR spectrum of *ca.* 0.2 mmol of commercial TBTH in [$^{2}H_8$]THF, (*b*) 46 MHz ^{2}H NMR spectrum of deuteriated TBTH in [$^{1}H_8$]THF and (*c*) 320 MHz ^{3}H NMR spectrum of tritiated TBTH. All spectra were acquired on the 5 mm tritium/proton dual probe of an IBM Instruments AF-300 NMR spectrometer system, with 8K data points, and the FID was Gaussian multiplied (LB = −1, Gb = 0.10) and zero-filled to 16K data points before Fourier transformation.

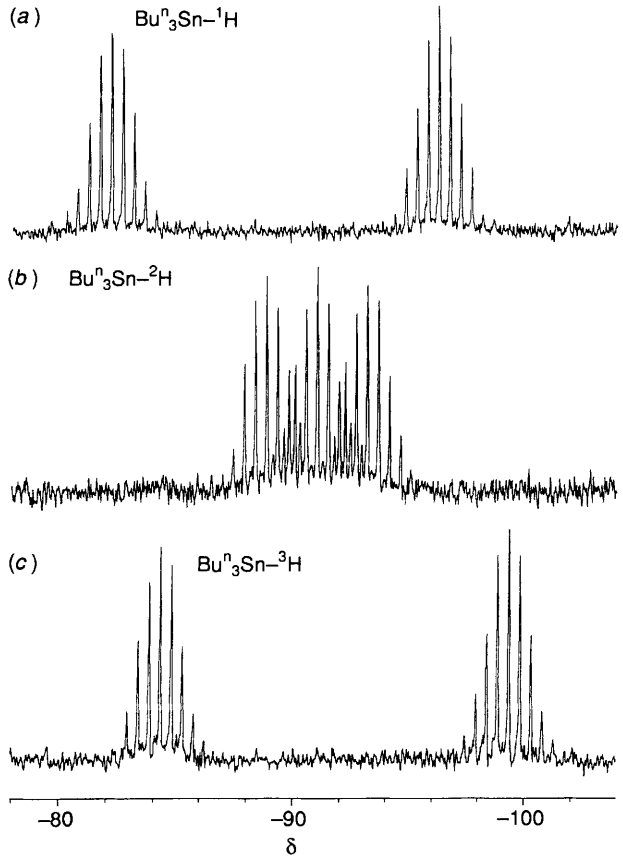

Fig. 2 111.9 MHz ^{119}Sn NMR spectra of the isotopic tri-n-butyltin hydride samples described in Fig. 1, with chemical shifts relative to tetramethyltin; (*a*) spectrum of *ca.* 0.2 mmol of commercial TBTH in [$^{2}H_8$]THF, (*b*) deuteriated TBTH in [$^{1}H_3$]THF and (*c*) tritiated TBTH in [$^{2}H_8$]THF. The 5 mm tubes from the experiments in Fig. 1 were held concentrically inside a 10 mm NMR tube, and spectra were acquired overnight (*ca.* 15 000 scans).

and solvent were removed by evacuation, and the solid was washed twice by injecting tetrahydrofuran (THF, 100 μl) and then evacuating the solvent. After the third addition of THF the pressure in the flask was adjusted to 80 kPa with dry nitrogen gas, tri-n-butyltin chloride (54 μl, 0.2 mmol) was injected, and a fine white precipitate of LiCl formed immediately. The mixture was stirred for 15 min, and the solvents were removed under vacuum. After addition and removal of another aliquot (800 μl) of THF, the $Bu^n_3Sn-^3H$ was dissolved in n-hexane (2 ml). The mixture was then filtered through a glass fibre filter to remove the LiCl, and the hexane was removed under a flow of N_2. The hydride was then dissolved in [$^{2}H_8$]THF for NMR study, and the solution was doubly contained inside a capped Teflon tube, inside a sealed glass tube.

The 300 MHz ^{1}H NMR spectrum of an equivalent amount of a commercial sample of TBTH dissolved in [$^{2}H_8$]THF is shown in Fig. 1(*a*). The spectrum has a singlet at δ 4.7 due to spin zero Sn–^{1}H species (83%), and small doublets for ^{117}Sn–^{1}H (7.67%, *J* 1505 Hz) and ^{119}Sn-^{1}H (8.68%, *J* 1575 Hz) species respectively (asterisked). The ^{119}Sn (111.9 MHz) NMR spectrum of this sample [Fig. 2(*a*)] showed a doublet of multiplets, with the multiplet structure arising from the long range ^{119}Sn–^{1}H couplings to the Bu^n groups, as expected. A deuterium sample was prepared according to the procedure above, using [$^{1}H_8$]THF as the final solvent, and the 46 MHz ^{2}H NMR spectrum is shown in Fig. 1(*b*). The major features are the deuteride peak at δ 4.7 and the ^{117}Sn and ^{119}Sn satellites [$J_{117Sn-2H}$ 231 Hz; $J_{119Sn-2H}$ 242 Hz]. The ^{119}Sn NMR spectrum of this sample [Fig. 2(*b*)] showed a triplet of multiplets, as expected from coupling to the spin = 1 deuterium nucleus. The 320 MHz ^{3}H NMR spectrum of $Bu^n_3Sn-^3H$ in [$^{2}H_8$]THF is shown in Fig. 1(*c*). The spectrum showed the large tritide singlet at δ 4.7, and small doublets for ^{117}Sn–^{3}H (*J* 1610 Hz) and ^{119}Sn–^{3}H (*J* 1685 Hz) species respectively. The ^{119}Sn spectrum [Fig. 2(*c*)] showed a doublet of multiplets, as expected. Comparison of the proton spectrum of the tritiated hydride reagent with that of the standard TBTH [Fig. 1(*a*)] suggested that the tritium substituted on the Sn atom was diluted with hydrogen by less than 2%.

One feature of the spectra in Fig. 2 is the primary isotope effect on the ^{119}Sn chemical shift, with the origin of the multiplets being moved to higher field with substitution by the heavier isotopes [*i.e.* Bu^n_3Sn-H −89.2 ppm, $Bu^n_3Sn-^2H$ −91.0 (Δδ −1.8 ppm), and $Bu^n_3Sn-^3H$ −91.9 ppm (Δδ −2.7 ppm)]. Both the direction and the magnitude of this isotope effect is as expected,[8a] and the chemical shifts, coupling constants and deuterium isotope effect for this compound have been reported previously.[8b] Our measured ^{119}Sn–^{1}H and ^{119}Sn–^{2}H coupling constants agree with the literature values within 2%, and our observed chemical shifts and isotope effects are very similar,[8] despite using THF as the NMR solvent rather than CCl_4 or C_6H_6. One new feature that may be significant is that the measured ^{117}Sn-^{3}H and ^{119}Sn-^{3}H coupling constants are larger (+4 Hz) than calculated from the analogous observed Sn-^{1}H constants. This effect is too small to be recorded in the case of the deuteriated molecule (*i.e.* the effect on *J* would be expected to be comparable with the digital resolution of the NMR experiment). Another feature of the ^{119}Sn spectrum of the tritiated sample was the appearance of a multiplet pattern

at δ −13 (*ca.* 10% of the total ^{119}Sn signal) which may be due to Bu^n_4Sn (in the range of −6 to −12 ppm depending on the solvent[9]), but is not from either $Bu^n_3Sn–SnBu^n_3$ (*ca.* −80 ppm[10]) or $Bu^n_3Sn–Cl$ (*ca.* 141 ppm[10]).§

The diversity of labelled pharmaceuticals required for research and clinical studies is driving the constant development of new or refined tritiation techniques, and the pressure to improve procedures is great. Having synthesized and characterized $Bu^n_3Sn–^3H$ at full S.A., we are currently applying it to the many possible reactions where it is used in everyday organic syntheses, and will report these results in a subsequent manuscript.

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§ *Note added in proof*: The ^{3}H NMR spectrum of $Bu^n_3Sn–^3H$ was the same after 24 h as for the freshly prepared reagent. Although we have no evidence of radiolyses effects on the reagent stability, we use the reagent immediately after preparation to minimize such possible effects.

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