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Synthesis of Phenylsilocane Tritium-Labeled at the Benzene Ring

V. V. Avrorin[a], G. E. Fominykh[a], I. S. Ignat'ev[a], E. N. Sinotova[a], and T. A. Kochina[a,b]

[a] *St. Petersburg State University, Chemical Department, Universitetskii pr. 26, St. Petersburg, 198504 Russia*
e-mail: radiochem@yandex.ru; t-kochina@mail.ru

[b] *Grebenshchikov Institute of Silicate Chemistry, Russian Academy of Sciences, St. Petersburg, Russia*

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Abstract—A strategy for synthesis of the 2-phenyl-2-hydro-1,3-oxa-6-aza-2-silacyclooctane doubly tritium-labeled (2,4- or 2,6-) at the benzene ring has been elaborated. The products are sources of the silyl cations having the atrane structure.

Keywords: phenylhydrosilocane, synthesis, tritium-labeled atrane

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Recently, special attention of chemists, physicians and agrochemists has been drawn to atranes, organic and inorganic derivatives of triethanolamine and diethanolamine, especially to silatranes and protatranes, which have already been applied in medicine and agriculture. Among them, compounds with pronounced antitumor effect [1, 2] as well as compounds protecting organism from harmful action of high-frequency electromagnetic radiation (computers, mobile phones, microwave ovens, radars, etc.) have been found [3]. Novel methods are required to investigate the mechanism of biological action of these compounds on living organisms and their pharmacokinetics. The most important of them utilizes the labeled compounds in preclinical studies of new biologically active compounds of atrane series (silatranes, germatranes, and protatranes). Besides, using tritium-labeled atranes can put insight into the fundamental problem of existence and reactivity of cations with the atrane structure $N(CH_2CH_2O)_3M^+$ (M = Si, Ge, Sn, and Pb), which can act as intermediates in reactions of metalatranes. Existence of these cations has been predicted theoretically [4–6], and they have been detected in the gas phase [7, 8] but they have never been found in the condensed phase so far. The possibility of existence of quasisilatranylium and germatranylium cations has not been even discussed. In this work we used the elaborated nuclear-chemical method [9, 10] based on β-decay of tritium in the corresponding tritium-labeled compound for generation and investigation of reactivity of the cations.

$$R_2T_2M \xrightarrow{\beta} R_2TM^+ \text{ (M= C, Si, Ge, Sn).}$$

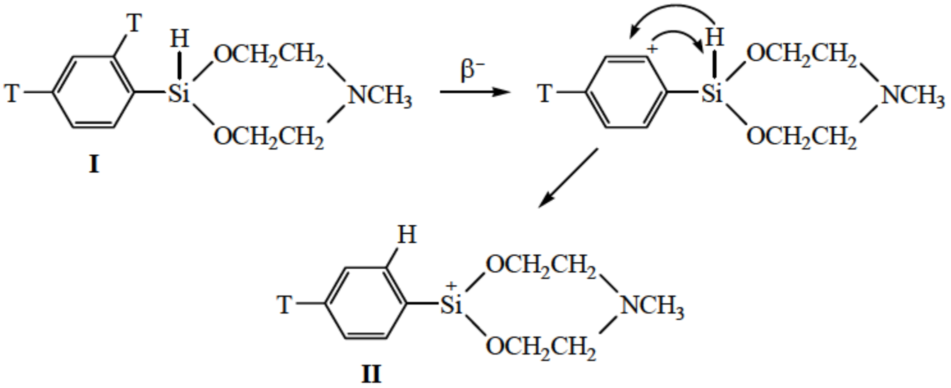
The presence of two or more tritium atoms in the compound resulted in formation of tritium-labeled cations, their further transformations (reaction with nucleophiles, isomerization, fragmentation, etc.) could be traced using radiochemical methods analyzing radioactivity of the final products.

We chose 2-(2,4-ditritiumphenyl)-2-hydro-1,3-oxa-6-aza-2-silacyclooctane (hereafter referred to as phenylsilocane) as a source of cations with atrane structure. Earlier, we demonstrated that β-decay of tritium in the *ortho*-position of the benzene ring in phenylsilane resulted in formation of phenylsilylium ion via the hydride shift [11]. The same effect was used for generation of silylium cations with atrane structure (Scheme 1).

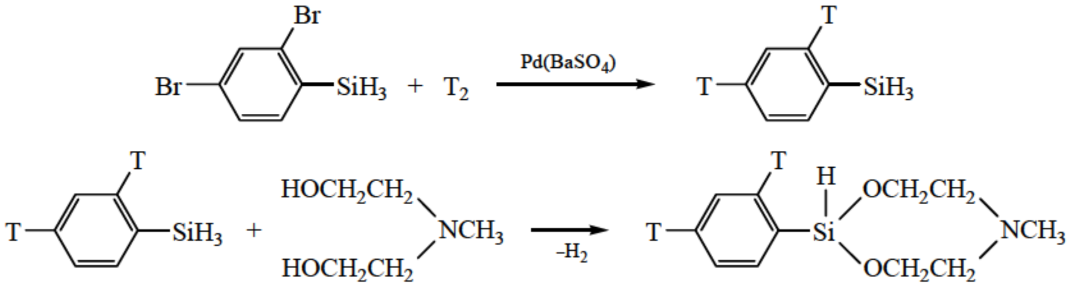
To do so, it was necessary to prepare a silocane (**I**) containing phenyl group and hydrogen atom at silicon. The phenyl group should be tritium-substituted at one or two *ortho*-positions. General scheme of synthesis of tritium-labeled phenylsilocane 2-(2,4-ditritiumphenyl)-2-hydro-1,3-oxa-6-aza-2-silacyclooctane **I** is given in Scheme 2.

2,4-Dibromophenylsilane was synthesized via the previously reported procedure [12]. Substitution of the halogen with tritium was performed via the reaction of

Scheme 1.



Scheme 2.



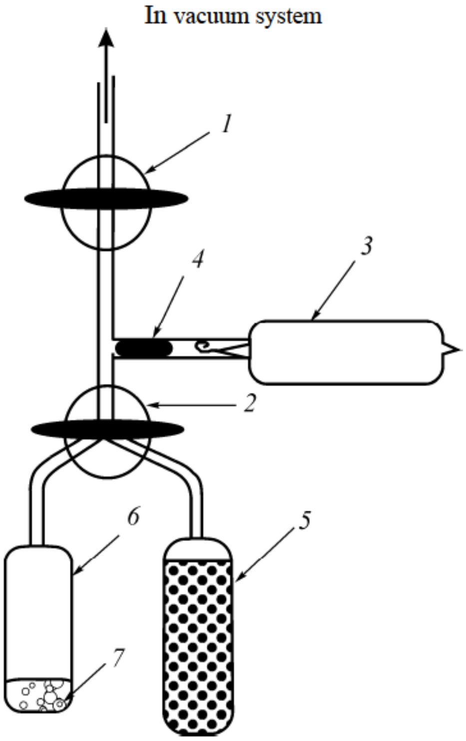
dibromophenylsilane with molecular hydrogen in hexane solution using the apparatus shown in the figure. The reaction vessel was charged with 5–10 mg of the catalyst (5% Pd on $BaSO_4$), the second vessel was filled with CaX molecular sieves. The both vessels were connected to vacuum pump and evacuated to ~10^{-3} mmHg; the vessel containing molecular sieves was heated to ≈400°C, and the reaction vessel was heated to ≈160°C. After the highest vacuum was reached, molecular hydrogen was introduced into the reaction vessel up to the pressure of about 0.5 atm; the vessel was incubated during 10–15 min at the reaction temperature, cooled down to room temperature, and residual hydrogen and volatile products were removed under vacuum. The reaction vessel was disconnected from the device, 50 μL of hexane solution containing 10 μmol of dibromophenylsilane and 30 μmol of triethylamine was added for fixation of the formed HBr. The vessel was again connected to the apparatus and evacuated at the temperature of liquid nitrogen. Molecular hydrogen (equivalent to ca. 2.5 Ci of tritium) was condensed into the vessel containing molecular sieves cooled by liquid nitrogen; the three-way stopcock was turned to connect the reaction vessel and the vessel with molecular sieves. The reaction vessel was cooled to –196°C, and the vessel with molecular sieves was warmed to room temperature. Then, the three-way stopcock was turned to isolate the reaction vessel, and its content was mixed by shaking during 1 h. The hexane solution was transferred to a vial sealed with rubber stopper. Piercing the stopper with the syringe needle, 10 μL of phenylsilane as the isotope carrier and 10 μL of *N*-methyldiethanolamine were successively introduced to the vial. The mixture was kept during 0.5 h at a boiling water bath and then cooled to room temperature; the formed phenylsilocane was isolated from the reaction mixture by high-performance liquid chromatography. Chromatographic separation was performed in a normal phase regime, using the column with inner diameter of 2.1 mm and length of 150 mm, filled with silica gel with grain size of 5 μm. 1% solution of acetonitrile in hexane was used as eluent at a flow rate of 0.5 mL/min, retention time of phenylsilocane was of 5.5 min. To isolate the silocane, the reaction mixture was applied to the column in 20 μL portions, and the eluent was collected at 5–6 min. Yield of the phenylsilocane calculated with respect to the introduced molecular hydrogen was of about 7%. The yield was fairly low but the amount of product was enough to generate the

Assignment of IR bands (cm^{-1}) in the spectrum of phenylsilocane based on the B3LYP/aug-cc-pVDZ simulation

ν_{exp}, cm^{-1}	ω_{calc}, cm^{-1}	Assignment	ν_{exp}, cm^{-1}	ω_{calc}, cm^{-1}	Assigment
3070	3193, 3183, 3174	ν(C–H, phenyl)	1213	1204	δ(C–CH, phenyl)
3047	3165, 3155			1193	
2940	3111	$\nu_{as}(CH_3)$		1172	δ(C–CH, phenyl)
	3094, 3082	$\nu_{as}(CH_2)$	1095	1142	ν(CO)
2878	3070	$\nu_{as}(CH_3)$	1095	1136	ν(SiC)
	3066, 3065	$\nu_{as}(CH_2)$	1076	1125	$\rho(CH_3)$
	2999, 2998, 2977, 2972	$\nu_s(CH_2)$	1038	1121	ν(CO)
2077	2190	ν(Si–H)		1092	δ(C–CH, phenyl)
1671, 1594	1634, 1608, 1507	ν(C–C, phenyl)		1086	$\rho(CH_2)$
1476	1491, 1489, 1483	$\delta(CH_2)$, $\delta_{as}(CH_3)$		1066	$\rho(CH_3)$
1463	1481	$\delta(CH_2)$	985	1066	$\rho(CH_2)$
	1475	$\delta_{as}(CH_3)$		1046	Δ[C–C–C(phenyl)]
	1455	$\delta(CH_2)$		1004	w(C–CH, phenyl)
1448	1445	ν(C–C, phenyl)	928	997	ν(C–C)
	1441	$\delta_s(CH_3)$		990	w(C–CH, phenyl)
1429	1398, 1383,	$w(CH_2)$		926, 896	$\rho(CH_2)$
	1374, 1368		900	890	
1354	1351	ν(C–C, phenyl)		860	w(C–CH, phenyl)
	1339	$\nu_{as}(NC_3)$	813	832, 832	δ(SiH)
1290	1322		780	762	$\nu_{as}(NC_3)$
	1312	ν(C–C, phenyl)		749	w(C–CH, phenyl)
1268	1279, 1274	$tw(CH_2)$	736	738	$\nu_{as}(SiO_2)$
1258	1227			713	δ(C–C–C, phenyl)
				708	w(C–CH, phenyl)
			693	664	$\nu_s(SiO_2)$
				629	δ(C–C–C, phenyl)

cation and to investigate its ion-molecular reactions with several substrates.

In our previous studies [13, 14] we have used dihalophenyltrialkoxysilane (converted into phenylsilane via the reaction with lithium aluminum hydride after introduction of radioactive label) as a starting compound for introduction of tritium at the benzene ring of phenylsilane. This avoided the isotopic exchange between tritium and the Si–H bond that could produce undesired labeling patterns in the benzene ring. Study of isotopic exchange between phenylsilane-D_3 ($C_6H_5SiD_3$) and molecular hydrogen under the conditions identical to those of halogen to tritium exchange showed that the precaution was not necessary. In particular, a hexane solution of phenylsilane-D_3 was stirred with the catalyst at room temperature during 2 h under hydrogen atmosphere. The solvent



Apparatus for synthesis of tritium-labeled phenylsilane. (*1*) vacuum gauge; (*2*) three-way stopcock; (*3*) ampoule with tritium; (*4*) magnetic striker; (*5*) ampoule with molecular sieves; (*6*) reaction vessel; and (*7*) reaction mixture and catalyst.

was removed under argon, the residue dissolved in deuterated chloroform, and ^{1}H NMR spectra of deuterated phenylsilane before and after the reaction of isotopic exchange were recorded. Intensity change of the SiH signal at 4.21 ppm was used as a measure of degree of isotopic exchange between the Si–H bond and molecular hydrogen. The intensity of the SiH signal in the both spectra was very low (within the instrument sensitivity), indicating no isotopic exchange occurring.

Phenylsilocane used as the isotopic carrier and containing no radioactive label, required for identification of the obtained labeled product by chromatography, was synthesized via the earlier-suggested procedure [15]. The prepared phenylsilocane was identified by the melting point (75–76°C) and its IR and NMR ^{1}H spectra. Assignment of the IR bands of phenylsilocane at 4000–600 cm^{-1} based on the B3LYP/aug-cc-pVDZ simulation is given in the table. The IR spectrum contained the Si–O stretching bands (736 cm^{-1}, ν_{as} SiO$_2$ and 693 cm^{-1}, ν_s SiO$_2$), the Si–H stretching band at 2077 cm^{-1} and the Si–Ar stretching band at 1076 cm^{-1}.

The NMR spectrum contained five groups of signals: a singlet at 2.43 ppm (3H), doubled triplets at 2.81 ppm (4H), a group of poorly resolved lines at 3.94 ppm (4H), a singlet at 5.15 ppm (1H), and two groups of signals at 7.2–7.6 ppm (5H). The spectrum corresponded to a structure containing a methyl group, two pairs of methylene groups, a SiH group, and a phenyl group; that was in line with the structure expected for **I**. The structure was further confirmed by the ^{13}C NMR spectrum that contained a weak signal of quaternary carbon atom of the phenyl ring, three signals assigned to *ortho*, *meta*, and *para* carbon atoms, two signals of methylene carbons, and a signal of a methyl group. The assignment was made using ^{13}C NMR spectrum in DEPT mode.

The calculated chemical ^{1}H shifts were in good agreement with the experimental data: CH$_3$, calc. 2.45 ppm (exp. 2.43 ppm); OCH$_2$, calc. 4.14 and 3.98 ppm (exp. 4.36 and 3.93 ppm); NCH$_2$, calc. 2.89 and 2.70 ppm (exp. 2.88 and 2.78 ppm); SiH, calc. 5.43 ppm (exp. 5.15 ppm); and Ph, calc. 7.53–7.65 ppm (exp. 7.2–7.6 ppm).

EXPERIMENTAL

Synthesis of 2,4-dibromophenyltrichlorosilane. A flask equipped with dropping funnel and a condenser with calcium chloride tube was charged with 32 mL (0.2 mol) of freshly distilled phenyltrichlorosilane and 200 mg of powdered iron. Then, 21 mL (0.4 mol) of bromine distilled over barium oxide was added dropwise upon stirring with a magnetic stirrer at 70–90°C within about 2 h. After that, the mixture was incubated at the reaction temperature for another hour, and a crude product was distilled off under reduced pressure collecting the fraction with bp of 110–150°C. 25 mL of pure product was obtained after redistillation in vacuum (bp 135°C at 2 mmHg).

Synthesis of 2,4-dibromophenylsilane. A flask equipped with dropping funnel and a condenser was charged with 2.5 g of finely-dispersed lithium hydride and 250 mL of anhydrous tetrahydrofuran. The mixture was stirred with a magnetic stirrer and then heated to slight boiling. 25 mL of dibromophenyltrichlorosilane was added dropwise to the hot mixture under constant stirring. The rate of addition was such that THF was boiling. After addition of the dibromophenyltrichlorosilane, the reaction mixture was refluxed during 1 h. The precipitate of LiCl and excess of LiH was separated by vacuum filtration, THF was removed, and the residue was distilled under water-jet pump vacuum collecting the fraction with bp of 120–140°C.

According to chromatography analysis and NMR spectroscopy data, the obtained product was a mixture of two isomers: 2,4- and 2,6-dibromophenylsilane in the ratio of 94–95% of 2,4-dibromophenylsilane to 5–6% of 2,6-dibromophenylsilane (GC).

Synthesis of phenylsilane and phenylsilane-D$_3$. Phenylsilane and its deuterated analog phenylsilane-D$_3$ were obtained via reduction of phenyltrichlorosilane with lithium hydride or lithium deuteride in tetrahydrofuran.

Synthesis of phenylhydrosilocane. 5 mL of phenylsilane was placed to a vial with a screwed mantle, rubber septum, and gas-removing tube; 5 mL of *N*-methyldiethanolamine was slowly introduced dropwise through the septum with syringe upon stirring with a magnetic stirrer. Vigorous hydrogen evolution and formation of a viscous solid product were immediately observed. After addition of the diethanolamine, the reaction mixture was heated at a boiling water bath during 1 h. The silocane was extracted from the reaction mixture with hot hexane. The hexane extract was evaporated and, after cooling, about 1 g of white crystalline compound was isolated (mp 76–78°C after recrystallization).

NMR spectra were recorded at the Research Resources Center for Magnetic Resonance of St. Petersburg State University using a Bruker 400 Avance spectrometer. IR spectra were recorded at the Center for Optical and Laser Materials Research of St. Petersburg State University using a Nicolet 8700 (Thermo Scientific) IR Fourier spectrometer.

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