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Modeling and Experiment Reveal an Unexpected Stereoelectronic Effect on Conformation and Scalar Couplings of α-Aminoorganostannanes, with Possible Relevance to the Tin−Lithium Exchange Reaction

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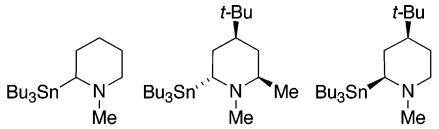
The solution conformation of *N*-methyl-2-(tributylstannyl)piperidines has been determined through the use of vicinal $^{119}Sn-^{13}C$ coupling constants, revealing a conformational distortion caused by an unexpected stereoelectronic effect in some cases. Specifically, the "equatorial" conformer is distorted into a half-chair, in which the nitrogen lone pair eclipses the C−Sn bond. This distortion, which "costs" approximately 1 kcal/mol, correlates with a conformational dependence of geminal $^{119}Sn-^{15}N$ couplings and a possible correlation with reactivity in the tin−lithium exchange reaction.

Central to the emergence of organolithiums as some of the most versatile reagents available for organic synthesis[1] has been the use of functionalized organolithiums in asymmetric synthesis. Among functionalized organolithiums, those having a nitrogen on the carbanionic carbon have developed into a tremendously useful class of compounds.[2] Among α-aminoorganolithium compounds, the so-called unstabilized class exhibits an interesting array of reactivities, including anionic cyclizations, sigmatropic rearrangements, and promiscuous reactivity in electrophilic substitutions.[2] They are configurationally stable in ethereal solvents[3] but epimerize in hydrocarbon−ether mixtures and, under the influence of chiral ligands, can undergo dynamic resolution in electrophilic substitutions.[4]

Because of the kinetic barrier to direct deprotonation, the most commonly used method for the generation of unstabilized α-aminoorganolithiums is tin−lithium exchange in α-aminoorganostannanes. Introduced by Peterson in the early 1970s,[5] this method has been used for the preparation of unstabilized primary[5,6] and secondary α-aminoorganolithiums,[3,7] as well as dipole stabilized α-aminoorganolithiums.[8] Because of their importance in the generation of α-aminoorganolithiums, α-aminoorganostannanes are an important class of compounds in their own right.

During our investigations of unstabilized α-aminoorganolithiums derived from α-aminoorganostannanes, we have noted some anomalies that appeared to us to reveal unexpected stereoelectronic effects on the conformational structure of some α-aminoorganostannanes. For example, *N*-methyl-2-(tributylstannyl)piperidine, **1**,



1 **2** **3**

was found to be a 55/45 mixture of two conformers instead of the expected 95/5 mixture (based on R_3Sn *A* values), when studied by NMR at slow exchange.[9] Further, we observed the failure of axially oriented tin in **2** to exchange for lithium, whereas **3** transmetalated readily.[10]

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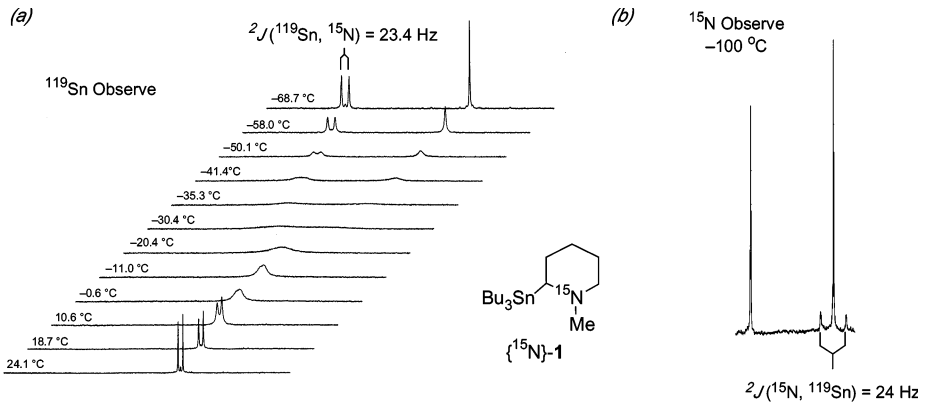


FIGURE 1. DNMR spectrum of {^{15}N} *N*-methyl-2-(tributylstannyl)piperidine, **1**, in Et_2O-d_{10}: (a) ^{119}Sn spectrum, (b) ^{15}N spectrum.

Because of the importance of the tin−lithium exchange to α-aminoorganolithium chemistry, we undertook a study of α-aminoorganostannane solution structure and report the results herein. This study has revealed a conformational effect that influences the magnitude of $^2J_{Sn-N}$ coupling constants. Interestingly, in two examples, we note that the magnitude of this coupling correlates with the success or failure of the Sn−Li exchange reaction. Furthermore, we have found that conformations of 2-(tributylstannyl)piperidines having the torsion angle between the nitrogen lone pair and the C−Sn bond synperiplanar (eclipsed) are stabilized by a stereoelectronic effect. Taken together, these observations hint at a subtle stereoelectronic effect that influences the rate of the Sn−Li exchange reaction.

Results

Nitrogen-15 enriched *N*-methyl-2-(tributylstannyl)piperidine, **1**, which was prepared in order to help establish the solution structure of *N*-methyl-2-lithiopiperidine,[11] exhibited a 14.8 Hz $^2J_{Sn-N}$ coupling at room temperature. To our surprise, the coupling vanished in one of the conformers at slow exchange, as shown in Figure 1. The coupling can be seen clearly in both the ^{119}Sn and ^{15}N spectra. In the latter, the coupling appears as satellites around one of the conformers.

To assign the conformers, we recorded the natural abundance ^{15}N NMR spectrum of two conformationally rigid stannyl piperidines, **2** and **3** (Figure 2). The absence of a coupling in axial stannane **2**, in which the tin is trans to the *tert*-butyl, and the presence of a 24 Hz coupling in the cis isomer **3** permit assignment of the coupled conformer in Figure 1 to the "equatorial" conformer. As will be shown below, this conformer is not a relaxed chair having the tin in a classical equatorial conformation.

To probe the solution conformation further, we prepared two rigid α-aminoorganostannanes, *N*-Boc-isoquinuclidine **6** and *N*-methylisoquinuclidine **7** (Scheme 1), whose torsion angles are obvious from molecular models, assigned the carbon NMR spectrum, and measured the $^3J_{Sn-C}$ coupling constants. Isoquinuclidine **4**[12] was acylated with Boc anhydride to afford **5** in 75% yield. Boc-isoquinuclidine **5** was formed as a mixture of rotamers

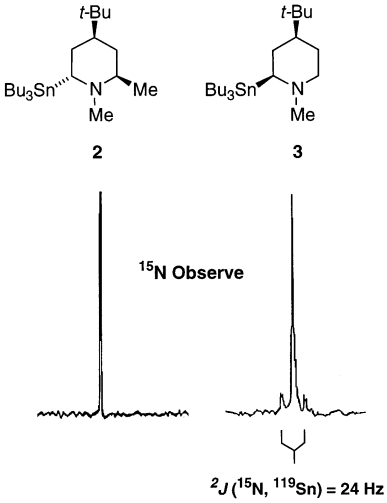
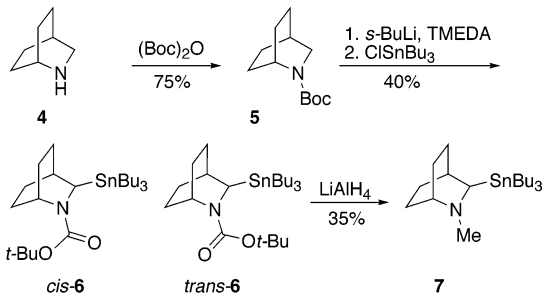


FIGURE 2. Natural abundance ^{15}N spectrum of *cis*- and *trans*-4-*tert*-butyl-2-(tributylstannyl)piperidines.

SCHEME 1



that did not interconvert on the NMR time scale. It was deprotonated and stannylated by the method of Beak,[13] but observation of the metalation process by NMR revealed that only one rotamer was deprotonated. This limitation of the Boc group as an activating agent for deprotonation α to nitrogen has been noted previously.[14] Thus, *N*-Boc stannane **6** was formed in only 40% yield, along with recovered **5**. Reduction to **7** was an unexpectedly low yielding reaction, and *N*-methylstannane **7** was somewhat unstable, as it exhibited significant decompo-

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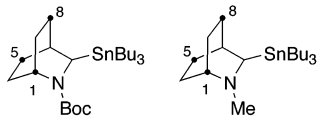
TABLE 1. Vicinal $^{119}Sn-^{13}C$ Coupling Constants and Associated Torsion Anglesg



6 **7**

compd	C no.	^3J, Hz	θ,[a] deg	compd	C no.	^3J, Hz	θ,[a] deg
6	1	11.8	114, 121	**7**	1	30.5	142
	5	52.7	178		5	62.5	167
	8	14.8	60, 63		8	12.0	74
					N-CH_3	5.8[b]	89

[a] Calculated with Macromodel 3.5 using the MM2* force field. The Bu_3Sn group was approximated by substituting a *tert*-butyl group with bond lengths constrained to 2.0 Å. The cis and trans conformers of **6** were both calculated, although only one set of carbon peaks was observed by NMR. [b] Line broadening effects due to the nitrogen were minimized using a Gaussian window function in order to resolve this small coupling.

sition, as observed by NMR (C_6D_6 solution) over 2−3 days. Nevertheless, sufficient quantities were obtained to record NMR spectra. The $^3J_{Sn-C}$ coupling constants were measured from the ^{13}C spectra, and the torsion angles were estimated by molecular mechanics calculations. The data are summarized in Table 1. Molecular mechanics calculations were used to estimate the torsion angles in stannylisoquinuclidines **6** and **7**. Although only one set of carbon signals was observed for urethane **6**, both rotamers were used in the calculations. The torsions differed slightly for carbons 1 and 8, and data for both are shown in Table 1.

Discussion

Since the seminal publications of Karplus over 40 years ago, organic chemists have used the relationship between $^3J_{H-H}$ (vicinal) coupling constants in proton NMR spectra and torsion angles to determine both structure and conformation.[15] Similar relationships have been derived for other spin $^1/_2$ nuclei. Most relevant to our purposes is the work of Kitching and colleagues,[16,17] who prepared a number of rigid monocyclic and bicyclic organostannanes and observed a "Karplus-like" relationship between the *Sn*−C−C−*C* torsion angle and the vicinal $^{119}Sn-^{13}C$ coupling constants, which can be described according to eq 1.[16,17]

$$^3J_{Sn-C} = 30.4 - 7.6 \cos + 25.2 \cos 2\theta \qquad (1)$$

The median deviation of the Kitching data to the curve described by eq 1 is 3.75 Hz,[16] which corresponds to a torsion angle of ±5°.

If this relationship were valid in these heterocycles, the magnitude of the $^3J_{Sn-C}$ coupling constant could be used to establish the conformations of stannylpiperidines **1**−**3** and to provide insight into the reasons for the small energy difference between the two conformers of **1**. However, the possibility exists that heteroatom lone pairs internal to, or proximal to, the four atoms involved in the vicinal coupling could affect the magnitude of the coupling.[18]

Figure 3 shows the original Kitching−Karplus (KK) data from carbocyclic stannanes, as well as the curve described by eq 1. Superimposed on this are the data from Table 1, where the coupling constants are known exactly and the torsion angles are known with reasonable accuracy. The data were evaluated by taking the MM2* torsions indicated in Table 1 and using eq 1 to solve for the expected coupling constants. Table 2 lists the couplings expected, and the difference between these calculated values and the observed values recorded in Table 1. For *N*-Boc isoquinuclidine **6**, the mean deviation of the calculated coupling constants is 6.5 Hz, which is somewhat larger than the mean deviation of the original Kitching data for carbocycles. Nevertheless, the mean deviation of the more relevant model compound, *N*-methylisoquinuclidine **7**, is 2.8 Hz, even less than the mean deviation of the Kitching data. The datapoint for the *N*-methyl carbon is in exceptionally close agreement with the measured value, but the computed torsion may not be as accurately modeled by the MM2* force field. Deleting it leaves a set of three points whose average deviation is 3.5 Hz, still well within the bounds of the KK data for carbocycles. We conclude that the Kitching−Karplus equation may be used to reliably evaluate torsion angles in piperidines, within the ±3.75 Hz (±5°) error limits of the original data.

Integration of the peaks in Figure 1 indicate an approximately 58:42 mixture of the two conformers at −69°. The coupling constant of **1** at 24.1 °C, 14.8 Hz, is a weighted average of the slow exchange coupling constants, 0 and 24, indicating a 62:38 ratio of the two conformers. These values are in reasonable agreement with the value of 55:45 obtained by integration of the carbon NMR spectrum at −70 °C.[9] The *A* values for trialkylstannyl groups are in the range of 1.0−1.1 kcal/mol.[19] If this value could be extrapolated to piperidines, as is true for alkyl substituents,[20] there should be approximately 90−95% of the equatorial conformer at equilibrium. The experiments described above indicate that only 55−62% of the more stable conformer is present at equilibrium, which translates to a free energy difference of only 0.11−0.29 kcal/mol at 278 K. Thus, there is an approximately 1 kcal/mol smaller difference in energy between these two *N*-methylpiperidine conformers and the energy difference between trialkylstannyl cyclohexane conformers.

It would seem that either the axial conformer must be stabilized or the equatorial confomer must be destabilized (or both) to account for the small energy difference. Having confirmed the validity of the KK relationship (eq 1) in 2-(tributylstannyl) nitrogen heterocycles, we may apply the relationship to piperidines **1**−**3**, to establish their solution conformation and perhaps gain some

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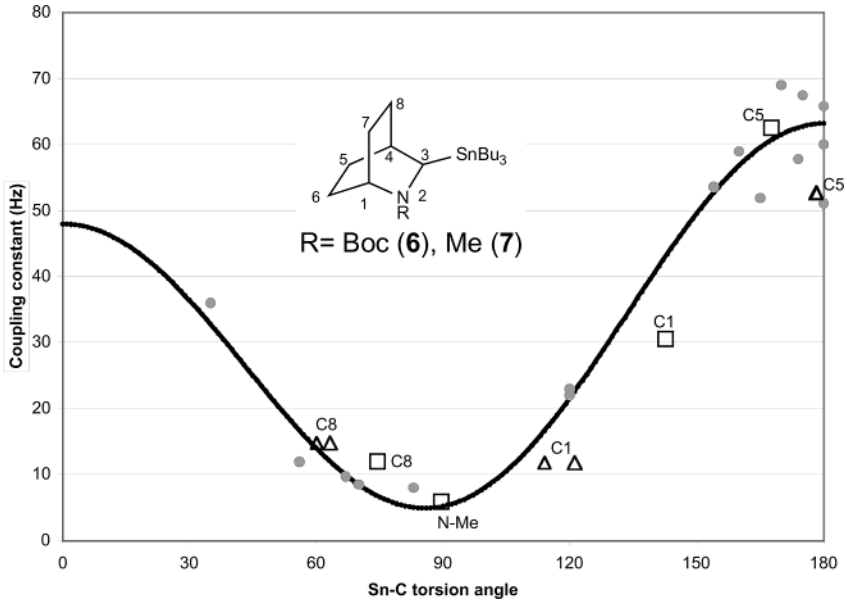


FIGURE 3. The solid line is the empirical Kitching−Karplus curve relating torsion angle to $^3J_{Sn-C}$ coupling constant in carbocycles (eq 1); the gray circles are the data from which the curve (eq 1) was derived. The triangles are the data for cis and trans **6**, and the squares are for **7** (Table 1).

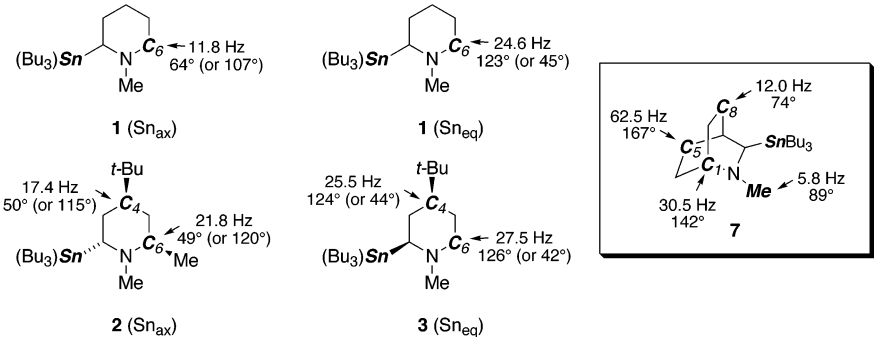
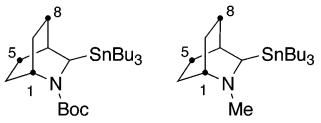


FIGURE 4. Couplings and torsions: For **1**−**3**, the couplings are measured and the computed Kitching−Karplus computed torsions are shown (±5°). Values in parentheses are the less likely solutions to eq 1. See the text for the rationale. Data for **7** from Table 1 shown for comparison.

TABLE 2. Vicinal ^{119}Sn−^{13}C Coupling Constants and Associated Torsion Angles



	6			**7**			
compd	C no.	J,[a] Hz	ΔJ,[b] Hz	compd	C no.	J,[a] Hz	ΔJ,[b] Hz
6	1	19.6	7.8	**7**	1	27.1	3.4
	5	63.2	10.5		5	60.5	2.0
	8	13.5	1.3		8	6.9	5.1
					N-CH_3	5.1	0.7

[a] Calculated from the Kitching−Karplus curve using eq 1 and the MM2* torsions in Table 1. Values for C1 and C8 for **6** are averages of the two rotomers. [b] Difference between observed coupling (Table 1) and KK value.

insight into the reasons for the small energy difference. In the following analysis, we use the data for the *N*-methylisoquinuclidine **7** for comparison to the *N*-methylpiperidines.

Figure 4 shows the observed coupling constants and the two solutions to the KK equation for each torsion, which are probably accurate to ±5°. Beginning with the conformation of **1** in which the tin is axial, the two solutions indicate possible torsions of 64° or 107°. Since 60° is expected for an axial substitutent, we assume 64° to be the correct solution. The axial tin in **2** appears to have a somewhat compressed torsion of 49° and 50° to C6 and C4, respectively (recalling that the KK error is ±5°), which may be due to the more highly substituted ring in this case. The observed coupling to C6 in the equatorial conformation of **1** shows possible torsions of 45° or 123°. Since a 45° torsion requires a boat conformation with the tin in a flagpole orientation, we take 123° as the correct solution. In equatorial stannane **3**, the couplings to C4 and C6 of 25.5 and 27.5, respectively, correspond to KK solutions of 124° and 126°. This example is particularly relevant when compared to values measured in the reference compounds **6** and **7** (Figure 4). Specifically, the antiperiplanar torsions to C5 in **6** and **7** result in 52.7 and 62.5 Hz couplings, respectively. Since this bond arrangement corresponds to the 25.5 Hz Sn−

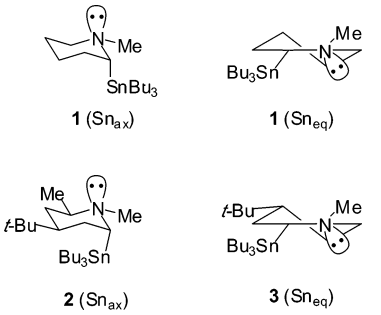


FIGURE 5.

C4 coupling in **3**, the two torsions cannot be similar. *That is, the Sn−C4 coupling in* **3** *cannot be antiperiplanar, the torsion that would be expected from a chair conformation with the tin in an equatorial position.* Comparing the 27.5 Hz Sn−C6 coupling in **3** with the 30.5 Hz Sn−C1 coupling in **7** shows that, in this case, the torsions *are* similarly anticlinal: 142° in **7** and 126° in **3**.

Figure 5 shows the conformations of **1**−**3** as deduced from the above arguments. The experimentally observed torsions reveal a half-chair conformation in which the C6−N/C2−C3 torsion is eclipsed in Sn_{eq} **1** and **3**, whereas Sn_{ax} **1** and **2** appear to be more "normal" chair conformations. The strain associated with the eclipsed conformation when the tributylstannyl group is "equatorial" is presumably responsible for the destabilization of the Sn_{eq} conformation of **1**. Note that Sn_{ax} **1** and **2** have the C2−Sn bond antiperiplanar to the nitrogen lone pair (assuming that the methyl is equatorial). In all of these compounds, the small (<9 Hz) coupling between the tin and the *N*-methyls suggests a torsion of near 90° between the Me−N and C−Sn bonds. This places the lone pair approximately synperiplanar (eclipsed) to the C2−Sn bond in Sn_{eq} **1** and **3** and antiperiplanar in Sn_{ax} **1** and **2**.

One possible explanation for the successful transmetalation of **3** and the failure of **2** may be that the nitrogen lone pair must be eclipsed (or nearly so) to the C−Sn bond and that prior coordination of the butyllithium to the lone pair is followed by oxidative addition of the butyl group to the tin, to form the -ate complex. Such an explanation is a "complex-induced proximity effect"[21] and is consistent with the fact that chelating heteroatoms facilitate transmetalation in at least one case where transmetalation fails.[22] Although this explanation suffices for this particular example, it does not explain the failure of acyclic α-aminoorganostannanes to transmetalate. One such example is compound **8**, discussed below.

The $^2J_{Sn-N}$ coupling observed for the piperidines having the tributylstannyl group in the "equatorial" configuration (for **3**) or conformation (for Sn_{eq} **1**) can now be seen

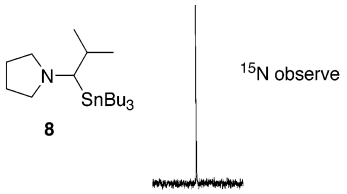


FIGURE 6.

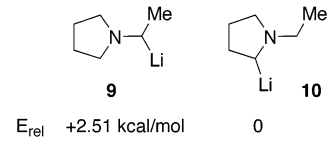


FIGURE 7. Relative energies at the RHF/3-21G level of theory.[23]

to arise when the lone pair and the C−Sn bond are eclipsed. Conversely, the $^2J_{Sn-N}$ coupling is absent when the lone pair and the C−Sn bond are antiperiplanar. These conclusions are interesting in light of the failure of **2** to transmetalate. Could it be that the stereoelectronic effect that influences conformation and $^2J_{Sn-N}$ coupling also influences tin−lithium exchange? To test this hypothesis, we recorded the natural abundance ^{15}N NMR spectrum of pyrrolidine **8** (Figure 6), a compound which is known to fail tin−lithium exchange.[23] No $^2J_{Sn-N}$ coupling was observed. Two data points (**2** and **8**) are insufficient to draw any conclusions, but it is intriguing to note the correlation, and we invite further investigation by theoreticians.

α-Aminoorganostannane **8** fails to transmetalate, even though one would expect that a conformation in which the nitrogen lone pair and the C−Sn bond are synperiplanar should be reasonably well populated. Model compounds **9** and **10** (Figure 7) were previously shown to differ by 2.51 kcal/mol at the RHF/3-21G level of theory,[23] suggesting that the traditional explanation of transmetalation failures in α-alkoxyorganostannanes, thermodynamic stability,[24] may also play a role here.

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Supporting Information Available: Experimental details, including spectra, for the synthesis of **6** and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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