0.5 μm for silica). Future studies will be aimed at more detailed product characterization and quantization of experimental parameters controlling particle formation and generation of intimate mixtures of substances by this nonequilibrium process.

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Lithium–Metalloid Exchange Reactions.[1] Observation of Lithium Pentaalkyl(aryl) Tin Ate Complexes

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The lithium–tin exchange reaction has become one of the premier methods for the preparation of vinyl-, aryl-, and even alkyllithium reagents in situations where other less expensive methods such as the reduction of halides or metalation are not selective or mild enough to be effective.[2,3] Although some kinetic work has been done,[4] the mechanism of this interesting transformation has not been established securely but has generally been assumed to proceed through a four-centered transition state. An alternative mechanism involving intermediate "ate" complexes has been proposed.[3] We have experimentally addressed the question of whether such previously undetected intermediates may actually be present in finite concentrations and offer here convincing spectroscopic evidence that this is the case.

Figure 1 shows a series of ^{119}Sn NMR spectra of THF solutions containing methyllithium and tetramethyltin (3:2) to which increasing amounts of HMPA were added. In pure THF only the tetramethyltin signal at 0 ppm was visible. As the concentration of HMPA was increased, a new signal at −277 ppm appeared[5] and grew at the expense of the tetramethyltin peak until that signal disappeared entirely. Careful analysis of the ^1H-coupled multiplet of both the normal and INEPT[6] spectra revealed that the best match between experimental and calculated line intensities occurs for a tin split equally by 15 protons.

Solutions of tetramethyltin and methyllithium in THF/HMPA show dynamic NMR behavior in the ^1H, ^{13}C, and ^{119}Sn spectra at temperatures between −80 and −20 °C. For example, the 270-MHz ^1H spectra of a solution 0.3 M CH_3Li, 0.16 M in $(CH_3)_4Sn$, and 0.4 M in HMPA showed broadening and partial coalescence of the signals assigned to CH_3Li, $(CH_3)_4Sn$, and a third species which we have identified on the basis of this and other spectroscopic evidence (Table I) as $Li^+Sn(CH_3)_5^-$. Although decomposition (formation of methane) and dramatic temperature dependence of the equilibrium constant complicate proper kinetic analysis of the spectra, they do serve to demonstrate that the three species are interconverted by an exchange process.

Solutions of mixed phenyl methyl complexes (**1**) were analogously prepared by the careful low temperature (<−80 °C) addition of the organostannane to methyl- or phenyllithium in

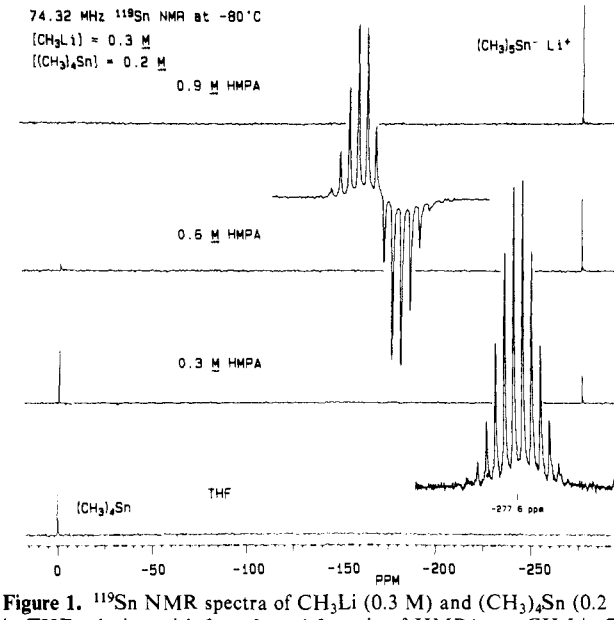
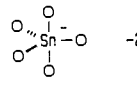
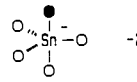
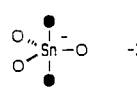
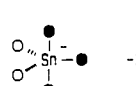
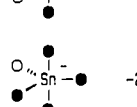
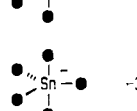


Figure 1. ^{119}Sn NMR spectra of CH_3Li (0.3 M) and $(CH_3)_4Sn$ (0.2 M) in THF solution with 0, 1, 2, and 3 equiv of HMPA per CH_3Li. The inset shows ^1H coupled expansions of the signal at −277 ppm using a normal and an INEPT[6] pulse sequence. Peak separation is 39 Hz.

Table I. Observed (Calculated) ^{13}C and ^{119}Sn Parameters for $Me_{5-m}Ph_mSn^-Li^+$ at −80 °C

● = C_6H_5 ○ = CH_3

Parameter:	δ_{Sn}	δ_C (Me)	$^1J_{Sn-Me}$	δ_C (Ph)[b]	$^1J_{Sn-Ph}$
Apical:[a]			(−17 Hz)	(180 ppm)	(80 Hz)
Equat:[a]			(441 Hz)	(151 ppm)	(640 Hz)
	-277	6.3	257 (258)	-	-
	-291	3.3	375 (327)	182.2 (180)	80 (80)
	-311	-1.0	450 (441)	180.0 (180)	60 (80)
	-300	-2.3	450 (441)	170.6 (170)	250 (267)
	-292	-2.3	436 (441)	165.0 (163)	376 (360)
	-303	-	-	161.9 (161)	427 (416)

[a] Parameters in parentheses were calculated by using the optimum axial and equatorial values listed at the top of each column. [b] C-1 of phenyl.

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$$Me_{4-n}Ph_nSn + RLi \underset{}{\overset{K_{eq}}{\rightleftharpoons}} \underset{\mathbf{1}}{Me_{5-m}Ph_mSn^-Li^+} \quad (1)$$
$$R = Ph, Me$$

THF/HMPA.[7] Again, the signal multiplicities and intensities were fully consistent with the structures expected from 1:1 complexation of organolithium reagent and organostannane.

We believe that our organotin "ate" complexes have trigonal-bipyramidal structures as do most main group hypervalent pentacoordinate compounds.[8] Each compound showed only a single set of phenyl and methyl resonances in the ^{13}C spectra at temperatures down to −80 °C, although two methyl or phenyl signals would have been expected for all except $Ph_2Me_3Sn^-Li^+$ if the compounds were not fluxional. Pseudorotation must therefore be fast on the NMR time scale.[9] Values of $^1J_{CSn}$ and δ were calculated by assigning optimal J and δ values to apical and equatorial groups and averaging the appropriate number of each type of ligand. This simple model provided predictions that agreed well with the experimental values listed in Table I. Reasonable results were obtained only when the phenyl group was assigned a higher apicophilicity than methyl.[10] A tetragonal-pyramidal model did not fit the observed data. The calculated $^1J_{CSn}$ values for both methyl and phenyl carbons were as expected: small coupling to apical (low s character) and large coupling to equatorial carbons.[11] The phenyl ipso carbon shifts were also interesting: the equatorial shifts are unexceptional while the apical phenyls are at 180 ppm, close to the value for phenyllithium.[12,13]

Some qualitative observations on the equilibrium constants between the various "ate" complexes and their dissociated species (eq 1) have been made. The fraction of "ate" complex increases as the number of phenyl ligands is increased: the relative concentration of higher phenyl homologues (**1**, m = 3–5) is substantial even in pure THF solution, but the lower phenyl homologues (m < 3) need HMPA to form.[14]

The observation of tin "ate" complexes under conditions that have typically been used in the preparation of lithium reagents via the Li/Sn exchange raises the question of whether these complexes or the lithium reagents in equilibrium with them are the actual reactive species.[3] We cannot as yet answer this question, but both qualitative and quantitative reactivity tests indicate that the "ate" complexes are substantially less reactive than lithium reagents toward electrophiles such as trimethylsilyl chloride, n-butyl iodide, and dimethyl disulfide.

Recent spectroscopic[3a,b] and chemical[3c] studies of (α-alkoxyalkyl)tin systems directed at the question of stable tin "ate" complexes have given negative or indefinite results. This is not surprising, since these studies were carried out in ether, THF, or DME solution with tributyltin compounds, conditions that we now know are not favorable for the formation of "ate" complexes in NMR-detectable amounts. The earliest evidence for a pentaorganostannate that we have been able to find is a 1954 report by Beermann and Hartmann[15] who proposed the formation of sodium triphenyldiethynylstannate during reaction of triphenylethynyltin with sodium acetylide. Several tetraorganostannate complexes have been recently described.[16]

Our studies provide solid evidence for the existence of hypervalent pentaorgano tin "ate" complexes and implicate them as intermediates in the Li/Sn exchange. These findings coupled with our earlier evidence for a similar intermediate in the Li/I exchange of aryl iodides[1a] suggest that hypervalent "ate" complexes may be generally involed in lithium-metalloid exchange reactions.[17]

Acknowledgment. We thank the Petroleum Research Fund, administered by the American Chemical Society, the National Science Foundation, and PPG Industries for support of our work. Dr. Bruce Adams provided valuable assistance in the design and execution of NMR experiments.

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Crystal and Molecular Structure of Methotrexate

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Methotrexate is a potent inhibitor of the reduction of dihydrofolate to tetrahydrofolate by dihydrofolate reductase (DHFR), an essential step in the synthesis of nucleotide bases, and is consequently a successful and widely used antitumour drug.[1] For some years a major effort has been directed toward the rational design of improved inhibitors of DHFR action.[2] It is believed that the greatly enhanced binding of methotrexate to DHFR compared to that of the natural substrate, dihydrofolate, is associated with protonation of different conformations of these ligands.[3] Thus, a knowledge of the ground-state structure and conformation of both inhibitors and substrates is required for this rational design of new inhibitors to be pursued. Considerable work has gone into establishing the preferred conformations of dihydrofolate reductase ligands by experimental and theoretical methods.[4,5] Despite many attempts to crystallize and structurally characterize such molecules, to date, none has been successful.

We report herein the crystallization and the determination of the crystal structure of methotrexate. The conformation is similar in some respects to that seen for methotrexate bound to DHFR

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