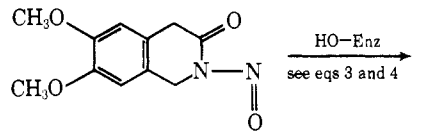
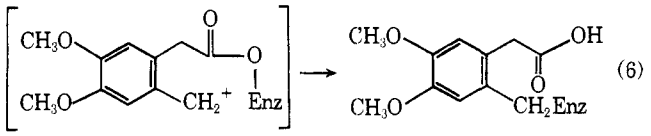
The low extent of inhibition observed is probably a result of diffusion of the carbonium ions away from the active site. To circumvent this difficulty, we turned to a cyclic analog (III),[4] in which the carbonium ion formed is prevented from diffusing away by its temporary attachment to the enzyme (through the acyl bond to the serine OH of chymotrypsin; IV, eq 6). Nitrosolactam III reacts with, and irreversibly in-



III



(6)

IV

hibits, chymotrypsin. In the presence of 4.6×10^{-5} M enzyme, a 1.2×10^{-3} M solution of III in 0.05 sodium phosphate buffer (containing 4% acetonitrile) at pH 7.9 and 20° is hydrolyzed >22 times faster than in the absence of the enzyme. The enzyme turns over 12 molar equiv of III within 5 min, and in this process becomes inhibited to the extent of ~98%. The inhibition is decreased in the presence of the competitive inhibitor hydrocinnamic acid (Table I), suggesting that the action of III is exerted at the active site.[9] The products of hydrolysis of III do not inhibit the enzyme (Table I). Treatment of the inhibited enzyme with hydroxylamine and/or dialysis does not regenerate activity, suggesting that the inhibition observed is not due to acylation.[10]

Inhibition of α-chymotrypsin with ^{14}C labeled III (at the NCH_2 position; activity 1.1×10^{10} (counts/min)/mol) and dialysis of the products led to labeled enzyme, the ^{14}C content of which showed that 1.6 mol of inhibitor had become bonded to 1 mol of the enzyme. Degradation of the inhibited enzyme to identify the labeled amino acid(s) is in progress.

In the inhibition of chymotrypsin outlined above, the substrate (nitrosolactam III) has little or no intrinsic derivatizing power for the enzyme; the active species for the inhibition ($C_6H_5CH_2^+$) is formed as a result of the enzyme "modifying" the substrate in the exercise of its normal catalytic function.[12,13] Inhibitor systems of this type favor derivatization of the functional groups at the active site relative to those elsewhere on the enzyme since the reactive groups are unmasked only at the active site.[13] Substrates analogous to I and III should function with trypsin, pepsin, papain, and other proteolytic enzymes. Further, oxidases could be labeled by this technique with substrates such as hydrazine derivatives that yield diazonium salts on oxidation. Reductases and other enzymes could presumably be derivatized by other suitable substrates and active species.

Acknowledgment. We thank the National Science Foundation (GP-8993) and the U.S. Public Health Service (Grant GM 21450) for financial support.

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Lithium 1,1-Dicyclopentadienyl-1-bromo-2,3,4,5-tetraphenylstannole, a Five-Coordinated Tin(IV) Heterocycle with Pseudorotating Axial- and Equitorial-Fluxional η^1-Cyclopentadienyl Groups in an $[R_4SnBr]^-$ Anion

Sir:

1,1-Dibromo-2,3,4,5-tetraphenylstannole [1] which is formed in 95% yield from phenyltin cleavage of hexaphenylstannole by elemental bromine at −40° in CCl_4 undergoes alkylation and complexation reactions typical of a diorganotin dibromide.[2] The expected dimethylstannole[3] results, for example, from treatment with methyllithium.

Treatment with excess lithium cyclopentadiene (from *n*-

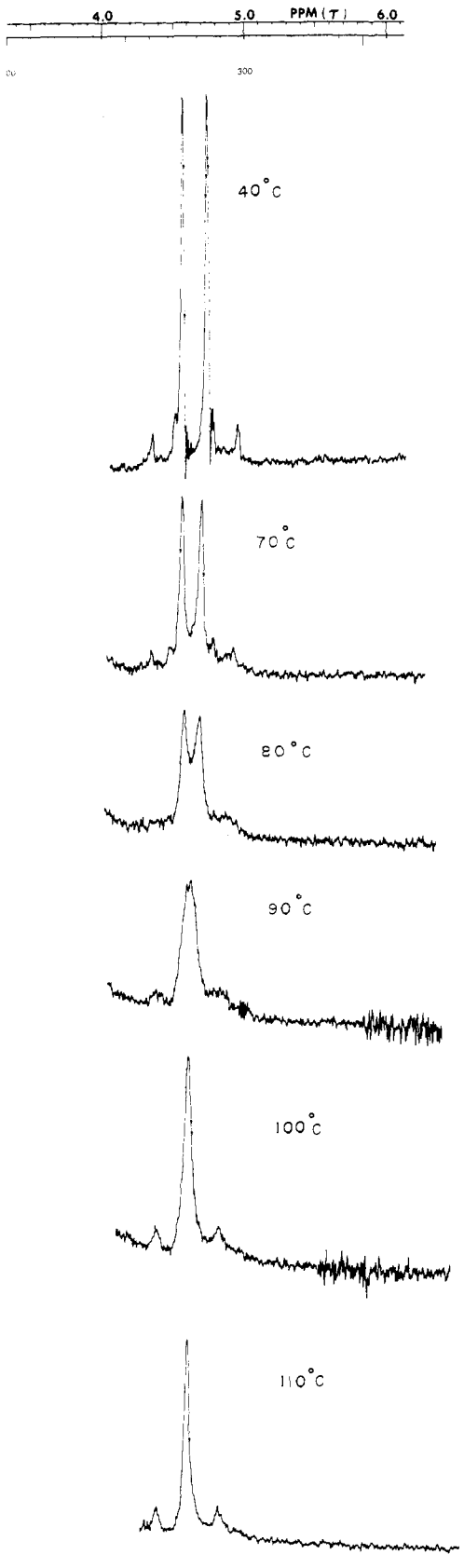


Figure 1. Variable temperature proton NMR spectrum of lithium 1,1-dicyclopentadienyl-1-bromo-2,3,4,5-tetraphenylstannole in toluene at 60 MHz.

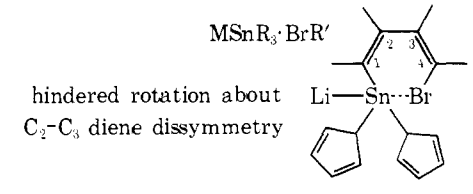
butyllithium and cylopentadiene monomer) at room temperature, followed by removal of the THF–hexane solvent and workup in toluene–hexane which precipitates Li Br, results, on the other hand, in the very slow formation of shiny, tan-colored, cubic crystals of the title compound (I) analyzing as $C_{38}H_{30}SnBrLi$[4] in 37% yield.

The proton and carbon-13 NMR spectra of (I) at room temperature appear similar, with two upfield resonances ascribable to the tin–cyclopentadienyl system (^1H 5.62 and 5.87 (toluene) or 5.72 and 5.94 ppm ($CDCl_3$), $J(^{117,119}Sn-^1H)$ = 25.4 Hz for both at 40°; ^{13}C 114.3 and 114.8 ppm (TMS standard), $J(^{117,119}Sn-^{13}C)$ = 30.2 and 26.2 Hz at ambient, respectively). The integration ratio (2.0:1 calcd; 2.5:1 found) reveals two cyclopentadiene groups per stannole ring. The derivative prepared from cyclopentadienylthallium also shows two resonances for the $(C_5H_5)_2Sn$ system (^1H 5.42 and 5.63 ppm, $J(^{117,119}Sn-^1H)$ = 26.0 Hz for both at 40°). Both resonances in the cyclopentadienyl region appear simultaneously from initial addition of C_5H_5Tl. The proton[5-7] and carbon-13[8,9] NMR data are consistent with those for analogous η^1-cyclopentadienyltin derivatives. For example, δ ^{13}C in the series of $(C_5H_5)_nSnR_{4-n}$ in which R = CH_3 and C_6H_5 and n = 1–4 lie in the range 113.6–114.3 with $(C_5H_5)_3SnCl$ at 114.8 ppm.[10] The tin–proton couplings in the related $(C_5H_5)_2SnBr_2$ (41.0)[11] and $(C_5H_5)_3SnCl$ (33.5)[11] with $J(^{117,119}Sn-^{13}C)$ = 26.0 Hz for the latter[10] are also similar to those for I.

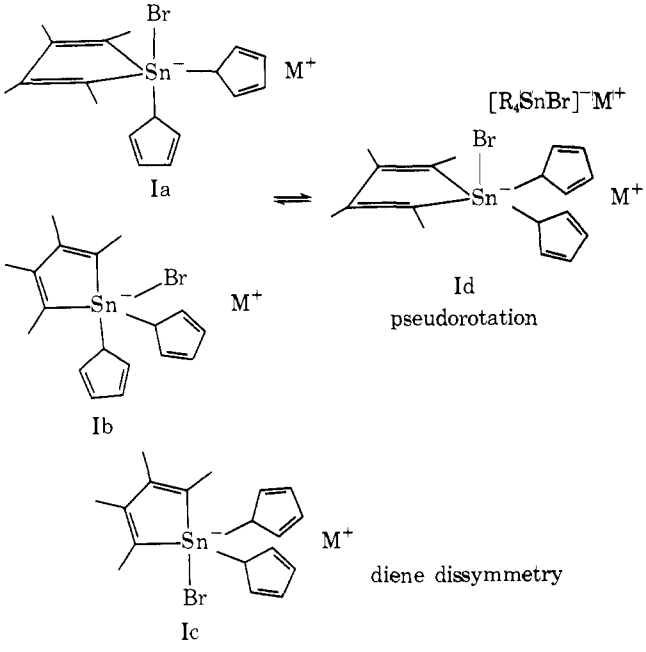
The infrared spectrum resembles that of the dibromostannole, but the two bands assigned to the tin–bromine stretch (ν_{asym} (253) and ν_{syn} (240 cm^{-1}))[2] are replaced by a single absorption of weaker intensity at 225 cm^{-1}. The new bands at 335 (s) and 332 (sh) cm^{-1} can be assigned to the ν_{sym} (Sn–C_5H_5) and ν_{sym} (Sn–C_5H_5), respectively, as found in $(C_5H_5)_4Sn$,[12] as well as in mixed cyclopentadienyltin methyl and phenyl derivatives.[10,13] Other absorptions above 3000 and between 1595 and 695 cm^{-1} specify the diene nature of the C_5H_5 ligands.[12,14]

The pair of proton resonances undergo only slight broadening at −100° consistent with previous studies on η^1-cyclopentadienyltin compounds in which fast, metallotropic, 1,2-shifts have been proposed.[7,9] However, as shown in Figure 1 the two equal intensity resonances exhibited at 40° merge into a single, unshifted peak at 90°. From the slope of the Arrhenius plot,[15] $\Delta E^{\ddagger}$ = 12.2 kcal/mol for the process. The tin–proton couplings associated with the two resonances remain relatively unchanged over the 210° temperature range studied.

Preservation of the couplings through the high-temperature region specifies an intramolecular process, and the lack of shift on changing temperature rules out an equilibrium process such as the dissociation of a dimer or ion pair. The origin of the cyclopentadienyl group nonequivalence may lie in hindered diene rotation in a $LiSnR_3$–BrR system arising from intramolecular Sn–Br coordination of the type thoroughly studied by Boer et al.[16-18]



However, I shows none of the properties of the triorganotin lithium compounds described in the literature.[19] Moreover, conductivity measurements over the concentration range 1.8 to 9 × 10^{-6} M gave Λ_0 = 123 ohm^{-1} $mole^{-1}$ cm^2 at infinite dilution in acetonitrile, characteristic of a weak 1:1 electrolyte. We are thus forced to consider the ionic formulations $[R_4SnBr]^-Li^+$ (Ia–d) based upon the conventional trigonal bipyramidal arrangement of ligands about tin.[20]



Conformers of the axially most-electronegative type (Ia) and in which the stannole ring spans one axial and one equatorial position (Ib)[21] can interconvert by a pseudorotation mechanism which may go through a tetragonal pyramid (Id) as shown.[22-24] Ic, combining both the axial-bromine and stannole ring spanning axial and equatorial positions, or the tetragonal pyramidal Id could give rise to the observed cyclopentadienyl group nonequivalence through a stannole ring nonplanarity. Such magnetic nonequivalence arising from a preferred dissymmetric diene conformation is proposed for the related (4-bromo-1,2,3,4-tetraphenyl-*cis,cis*-1,3-butadienyl)dimethyltin bromide,[16-18] but is less likely for I. Formulation of a lithium ion association with the stannole ring in dicyclopentadienylstannole with a bromide counterion which would rationalize the temperature-dependent spectra in terms of a dissociation of the complex is ruled out by the lack of chemical shift dependence on temperature, and by the presence of a tin–bromide shift in the infrared. Chemical shifts are sensitive to the metal ion, Li^+ or Tl^+, however, and the lack of appreciable conductivity in nitrobenzene suggests significant ion pairing.

The synthesis of I can proceed through either 1-bromo-1-cyclopentadienylstannole followed by adduct formation with $C_5H_5^-$ anion or dicyclopentadienylstannole with subsequent bromide ion uptake. The appearance of both cyclopentadienyltin resonances from the onset of reaction argues against the former.

Tetraorganotin compounds show no Lewis acidity, yet the as yet unisolated 1,1-dicyclopentadienyl-2,3,4,5-tetraphenylstannole apparently takes up bromide ion during its formation from lithium or thallium cyclopentadiene in THF–hexane to give the $[R_4SnBr]^-$ anion rather than precipitating the metal bromide.[25]

Acidity studies on other cyclopentadienyltin derivatives are proceeding.

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(21) Based on these structures and hybridization arguments, the downfield resonance in the carbon-13 spectrum which has the smaller $J(^{117,119}Sn-^{13}C)$ value can be assigned to the axial-cyclopentadiene group. The tin coupling in the proton spectrum is smaller for the downfield resonance only at lower temperatures.
(22) Pseudorotation about either of the tin attachments to the stannole ring as a pivot would place the ring in a diequatorial position with a stannole angle C–Sn–C = 120°. Such an expansion of the ring angle at tin would be accompanied by considerable strain.
(23) Square pyramidal intermediates have been proposed to rationalize the temperature-dependent proton NMR of 2-biphenylbis(4,4′-bitolyl)antimony whose singlet methyl resonance collapes to a quartet at −60° ($\Delta E^{\ddagger}$ = 11.6 kcal/mol) (D. Hellwinkel and M. Bach, *Naturwissenschaften*, **56**, 214 (1969); *J. Organomet. Chem.*, **17**, 389 (1969)).
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Protonated Chloromethyl Alcohol and Chloromethyl Ethers. Proof for the Intermediacy of the Elusive Chloromethyl Alcohol[1]

Sir:

Chloromethyl alcohol, although suggested to be an intermediate in chloromethylation with formaldehyde and hydrogen chloride,[2] was not directly observed or substantiated by any evidence.

Encouraged by our previous preparation and study of protonated fluoromethyl alcohol,[3] we have extended our investigations and report now our success in directly observing (by low temperature NMR spectroscopy) protonated chloromethyl alcohol and a series of related protonated chloromethyl ethers.

A clean solution of protonated chloromethyl alcohol **1** was obtained when anhydrous HCl was introduced into a