of cyclohexane in a quartz tube, and argon was bubbled through the suspension for 30 min. The mixture was then irradiated for 15 h at 300 nm in a Rayonet RPR-100 chamber reactor. Filtration, concentration of the filtrate under reduced pressure and filtration through a short column of Celite gave 0.19 g (90%) of benoxaprofen methyl ester, mp 91–93 °C, identical in all respects with an authentic sample.[13]

Benoxaprofen (3). Benoxaprofen methyl ester (180 mg) was dissolved in 10 mL of 5% methanolic potassium hydroxide and the mixture was heated under reflux for 30 min. The solvent was then removed under reduced pressure, and the remaining solid was dissolved in water. Addition of HCl led to the separation of a heavy white precipitate which was collected by filtration and recrystallized from ethanol to give 152 mg (75%) of benoxaprofen, mp 188.5–190 °C, identical in all respects with an authentic sample.[13]

Registry No. 3, 51234-28-7; 4, 17408-16-1; 5, 101010-08-6; 6, 101010-09-7; 7, 101010-10-0; 8, 101010-11-1; a, 95-21-6; b, 833-50-1; c, 5676-58-4; d, 53012-61-6; e, 1141-35-1; *o*-$AcNHC_6H_4Tl(TFA)_2$, 101010-04-2; *o*-$PhCONHC_6H_4Tl(TFA)_2$, 101010-05-3; 4-Me-2-$AcNHC_6H_3Tl(TFA)_2$, 101010-06-4; 5-Me-2-$AcNHC_6H_3Tl(TFA)_2$, 101010-07-5; *p*-ClC_6H_4-*o*-$CONHC_6H_4Tl(TFA)_2$, 101030-87-9; *m*-$EtOCC_6H_4NH_2$, 1197-05-3; *p*-ClC_6H_4COCl, 122-01-0.

A ^{199}Hg NMR Study of the Complexation of Methylmercury with Thia-Crown Ethers. The Absence of a Macrocyclic Ligand Effect

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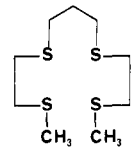
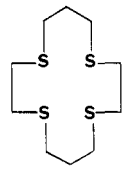
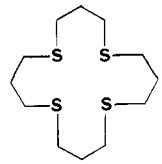
Macrocyclic multidentate ligands typically form more stable complexes with metals than their corresponding acyclic analogues. This *macrocyclic effect* in the homologous series of ligands that comprise the polythia cyclic ethers has been attributed by Rorabacher to the more favorable entropy associated with less flexible cyclic ligands.[1a] This group has also established that a 16-membered cyclic tetrathiaether ([16]aneS$_4$) is required to provide a cavity large enough for the Hg^{II} ion.[1b] An X-ray study on such a "crown-like" complex showed the Hg^{II} ion to be completely circumscribed by the macrocyclic ligand.[1b] Of particular relevance to the present study, it was also reported that open-chain complexes of $Hg(ClO_4)_2$ in $MeOH–H_2O$ solvent were more stable than their macrocyclic thia-crown counterparts.

As part of a related study aimed at designing an effective therapeutic agent for CH_3Hg^{II}, we have measured the formation constants for the complexation of CH_3HgX with a variety of sulfur-containing ligands.[2] This ^{199}Hg NMR method has now been extended to include the quantitative measurement of the K_f for $CH_3HgOCOCF_3$ with a series of cyclic and acyclic thiaethers. The data in Table I clearly demonstrate that simple sulfides and disulfides exhibit a surprisingly low affinity for CH_3Hg^{II} and that the proclivity for complexation with an acyclic dithiaether is at least 2 orders of magnitude greater than a 16-membered macrocyclic tetrathiaether.

The formation constants were measured by evaluating a least-squares fit of ^{199}Hg NMR data as described previously.[2] As anticipated, the K_f for interaction of the relatively ionic $CH_3HgOCOCF_3$ with di-*n*-butyl sulfide is much higher in methanol solvent than in methylene chloride.[2] The extent of complexation of $CH_3HgOCOCF_3$ is apparently much less than that with $Hg(ClO_4)_2$ ($CH_3OH–H_2O$) where a log K_f = 10.48 was noted for the [16]-aneS$_4$ thia-crown and 9.55 for the [14]-aneS$_4$ ligand.[1b] These data tend to contradict liquid–liquid extraction data in 1,2-dichloroethane solution where $HgSO_4$ and CH_3HgSO_4 exhibited a comparable electrophilicity toward [14]-aneS$_4$ thia-crown.[3] Our data, which were measured in CH_2Cl_2 for solubility purposes, also demonstrate that a dithiaether is a slightly more effective ligand than a linear acyclic tetrathiaether. This trend may be ascribed to an entropy effect associated with conformational rigidity required for "encapsulating" the CH_3Hg^{II} with all four sulfur donor atoms. The striking decline in the efficacy of the donicity of the cyclic thiaethers, irrespective of ring size, is much more difficult to explain. Since an absence of the classical macrocyclic effect has also been observed with Hg^{II} in $CH_3OH–H_2O$,[1b] this phenomenon cannot be attributed to the methyl group or to solvent polarity. These observations remain an enigma that awaits a more definitive theory and suggests that macrocyclic thiaethers would not suffice as effective antidotes for methylmercury poisoning. The striking difference between the affinity of a mercaptide ion[4] (RS^-) where $K_f = 10^{14}–10^{16}$ and a sulfide or disulfide toward CH_3Hg^{II} is also worthy of note.

Table I. Formation Constants for

$$CH_3HgOCOCF_3 + L \overset{K_f}{\rightleftharpoons} CH_3HgOCOCF_3{\cdot}L$$

ligand	K_f	solvent
CH_3SSCH_3	0.07	CH_2Cl_2
$(n\text{-}Bu)_2S$	0.07	CH_2Cl_2
$(n\text{-}Bu)_2S$	50	CH_3OH
$CH_3S(CH_2)_3SCH_3$	67	CH_2Cl_2
	45	CH_2Cl_2
 [14]-ane S$_4$	0.25	CH_2Cl_2
 [16]-ane S$_4$	0.36	CH_2Cl_2

Measurement of Equilibrium Constants

The sensitivity of the ^{199}Hg nucleus to both its primary ligands and the immediate solvation shell surrounding the metal is reflected in the range of chemical shifts that extend over 4000 ppm. Thus even relatively small formation constants K_f can be precisely determined by measuring the

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change in ^{199}Hg chemical shift upon complexation with a ligand. We have previously utilized this sensitive analytical probe to accurately measure the complexation of MeHgOAc and $CH_3HgOCOCF_3$ with a variety of ligands.[2,7] This is now a well-established procedure and application of this method to other problems has been demonstrated by several groups.[8]

For the equilibrium involving the interaction of MeHgX with added ligand L to form complex X, it follows that

$$\underset{(a-x)}{\mathrm{MeHgX}} + \underset{(b-x)}{\mathrm{L}} \overset{K_f}{\rightleftharpoons} \underset{(x)}{\mathrm{MeHgX{\cdot}L}}$$

if one assumes no prior dissociation or association of the reactants. Since equilibrium is attained rapidly on the NMR time scale, only one mercury resonance is observed, which is a weighted average of the chemical shifts of the free and the complexed metal species in solution.

$$\delta_{obsd} = \Delta\delta + \delta_0 = \delta_0\chi_m + \delta_X\chi_{ML}$$

where δ_0 = chemical shift of uncomplexed metal, δ_X = chemical shift of fully complexed metal, $\Delta\delta = \delta_{obsd} - \delta_0$, χ_M = mole fraction of free metal = $(a-x)/a$, and χ_{ML} = mole fraction of complexed metal = x/a.

If the initial concentration of MeHgX is held constant, then the concentration of the complex (x) may be expressed in terms of (x/a), the molar ratio of the complex to initial concentration of MeHgX. When an equilibrium involved is such that $b \gg a$ and/or K_f is very small, then the reciprocal of the ligand induced change in ^{199}Hg chemical shift, $\Delta\delta^{-1}$, is linearly related to the reciprocal of the ligand concentration, b^{-1}, such that

$$\Delta\delta^{-1} = K_f^{-1}(\delta_X - \delta_0)^{-1}b^{-1} + (\delta_X - \delta_0)^{-1} \quad (1)$$

When the formation constants are relatively large and a large excess of ligand b cannot be attained, then a quadratic expression in terms of $(a - x/a)$ as described by Popov[9] may be utilized as follows

$$\delta_{obsd} = \Delta\delta + \delta_0 = \frac{1}{2K_a}(-(D)^{1/2} + (D + 4K_a)^{1/2})(\delta_0 - \delta_X) + \delta_X \quad (2)$$

where $D = (K_b - K_a + 1)^2$.

This equation has also been used by Kan[10a] and Marzilli[10b] in their investigation of the complexation of Hg^{2+} with nucleosides by using ^1H and ^{13}C NMR. The procedure employed in the evaluation of K_f is to substitute the experimental parameters $\Delta\delta$, δ_0 (the initial chemical shift of a), a and b and vary the two adjustable parameters K_f and δ_X (the chemical shift of fully complexed a) until the calculated chemical shifts correspond to the experimental $\Delta\delta$ values within given error limits. The general non-linear curve-fitting program KINFIT-4[11] was used with the appropriate equations.[2,7]

Experimental Section

Dimethyl disulfide and di-*n*-butyl sulfide were commercially obtained and distilled before use. The acyclic and cyclic polythiaethers were prepared according to the procedure of Rosen.[5] The $CH_3HgOCOCF_3$ was prepared as described previously.[6]

Measurement of ^{199}Hg Spectra. The ^{199}Hg spectra were measured by using a Nicolet NT-300 spectrometer at a frequency of 53.712282 MHz, with a 20-μs pulse width and a 250-ms post-acquisition delay using a ±35714.2-Hz spectral width. Ten millimeter sample tubes were used with a 0.10 M solution of $CH_3HgOCOCF_3$ in 50% $CDCl_3$ or CH_3OD as an internal lock solvent. The spectra represent 4096 scans with a ^1H-decoupling frequency of 300.058421 MHz. Neat $(CH_3)_2Hg$ in a concentric capillary tube was used as an external standard.

Registry No. $CH_3HgOCOCF_3{\cdot}CH_3SSCH_3$, 100909-39-5; $CH_3HgOCOCF_3{\cdot}(n\text{-}Bu)_2S$, 100909-40-8; $CH_3HgOCOCF_3{\cdot}CH_3(CH_2)_3SCH_3$, 100909-41-9; $CH_3HgOCOCF_3{\cdot}CH_3S(CH_2)_2S(CH_2)_3S(CH_2)_2SCH_3$, 100909-42-0; $CH_3HgOCOCF_3{\cdot}(14\text{-}AneS_4)$, 100909-43-1; $CH_3HgOCOCF_3{\cdot}(16\text{-}AneS_4)$, 100909-44-2.

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Large-Scale Synthesis of Pinacol Iodomethaneboronate and Its Application to (Acylamino)methaneboronates via (Trimethylsilyl)lithioamines

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Significant biological activity has been observed with a number of aminomethaneboronates recently reported as analogues of α-amino acids. For example, certain aminomethaneboronates have been prepared which are potent transition-state inhibitors of α-chymotrypsin,[1] while another aminomethaneboronate has been identified as a potential neutron capture agent for treatment of malignant melanoma.[2] Furthermore, some boronate complexes can move across living membranes,[3] adding to the biological potential for this area. Although a variety of methodology exists for introducing the boronate moiety into organic molecules, few procedures are available to prepare (acylamino)methaneboronates.[1] We report an improved synthesis of pinacol iodomethaneboronate (**3**) and describe its application to the preparation of (acylamino)methaneboronates via (trimethylsilyl)lithioamines.

Several procedures to prepare pinacol iodomethaneboronate (**3**) were found in the literature,[4-6] one of which was reported during the course of this work.[6] Initially, though, we tried to prepare **3** using one of Matteson's procedures[5] and found the reaction to work well only on a small scale (~10 g). On several occasions we tried to scale up the reaction sequence to produce over 100 g of **3**. Isolation by vacuum distillation always afforded a poor yield of the iodide **3** with the rest of the material being sulfide **1**, yet GLC analysis before distillation showed only

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