The attractive interaction is also expected to effect the selective enantioface differentiation of the olefin to give high optical yields.[20]

(20) The (aminoalkyl)ferrocenylphosphines **1** were also found to be effective for the asymmetric hydrogenation of other types of acrylic acids such as atropic acid and α-methylcinnamic acid to give the products of over 80% ee.

Macrocycles Containing Tin. Through Space Cooperative Binding and High Size Selectivity in the Complexation of Chloride Ion by Lewis Acidic Macrobicyclic Hosts

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Received August 3, 1987

The interaction of basic macrocyclic and macrobicyclic hosts with cationic guests has been studied intensively in recent years. In contrast, the analogous complexation of anionic guests by Lewis acidic polydentate or macrocyclic hosts has received little attention.[1] Recently, we found low selectivity in binding of chloride ion in organic solvents by a series of macrocyclic hosts containing two Lewis acidic tin atoms.[2] We anticipated that the addition of more binding sites to or the incorporation of structural rigidity into our Lewis acidic macrocyclic hosts would result in more selective anion complexation. Creation of macrobicycles **1** appeared to be one way to build up binding site rigidity rapidly since Lewis acidic tin atoms containing one electron withdrawing group will complex donors in a trigonal-bipyramidal structure with the donor and withdrawing groups in the axial positions.[3] In this communication we report neutral Lewis acidic macrobicycles in which both the dynamics and energetics of binding of chloride anion are highly size dependent; this apparently represents selective binding of chloride within the host cavity in a manner directly analogous to the binding of cations by cryptands.[4]

The reaction sequence for preparation of macrobicyclic hosts **1** from macrocycles is shown in Scheme I. The starting macrocycles have been reported[5] as has the immediate precursor of **1b**.[6] The macrobicyclization reactions were effected in 20–30% yields for the precursors of **1b–d** but only in 4% yield for the (apparently) strained precursor to **1a**. The final HCl cleavage reactions were virtually quantitative. Sharp melting products **1** were characterized by ^1H, ^{13}C, and ^{119}Sn NMR spectroscopy.

The complexation of chloride by hosts **1** was studied by ^{119}Sn NMR spectroscopy.[7] Previously, we observed that macrocyclic hosts **2** exchanged chloride fast on the ^{119}Sn NMR time scale and that the first and second binding constants for hosts **2** were nearly

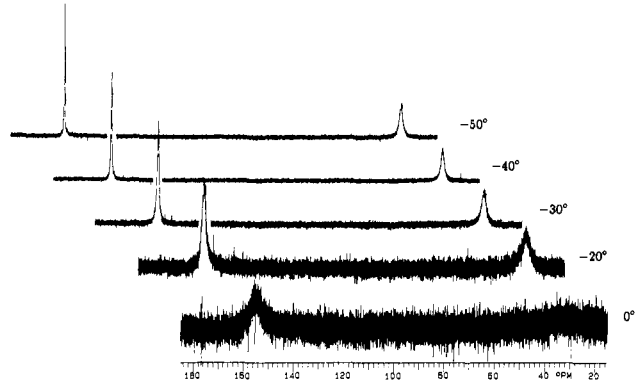
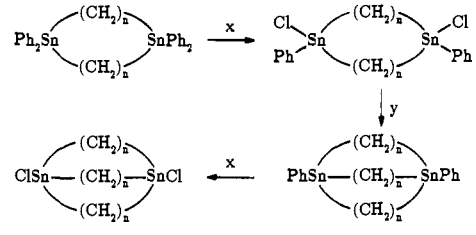


Figure 1. ^{119}Sn NMR spectra (149.2 MHz) of a $CDCl_3$ solution containing host **1b** and 0.5 equiv of tetrahexylammonium chloride.

Scheme I

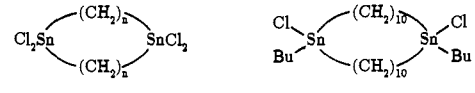


1

(a: n = 6, b: n = 8, c: n = 10, d: n = 12)

Reagents: x, HCl in CH_2Cl_2; y, $BrMg(CH_2)_nMgBr$ in THF.

the same for each host and varied little between hosts.[2] In this work, similar behavior was observed for macrocyclic model **3** in the binding of chloride in $CDCl_3$ solution; addition of increments of tetrahexylammonium chloride to a solution of **3** resulted in a smooth shift for the single sharp peak from +150 ppm (tetracoordinate) to −50 ppm (pentacoordinate).[8] Thus, model **3** (like hosts **2**) binds two chloride ions strongly and equilibrates rapidly ($k > 5 \times 10^6$ s^{-1}).



2 (n = 8, 10, 12) 3

The ^{119}Sn NMR spectra of bicyclic hosts **1** showed dramatic differences in comparison to those of their macrocyclic counterparts when chloride ion was present. Unlike macrocycles **2** and **3**, bicyclic hosts **1b–d** in the presence of excess chloride bound only one chloride per host; the limiting chemical shifts were at about the midpoint of the tetra- and pentacoordinate tin shifts (one signal for the two tin atoms arises either from fast exchange within the complex or complexation of chloride by both tin atoms simultaneously). There was no indication that any host **1** bound a second chloride anion. Thus, since the tin atoms are insulated from one another by hydrocarbon chains, there is a through space cooperative binding effect in **1b–d** mandated by the structure.

The rates of binding of chloride by hosts **1** were substantially slower than those for cycles **2** and **3**. In the presence of 0.5 equiv of chloride ion per host, the ^{119}Sn NMR spectra of C-12 host **1d** at room temperature consisted of one broad signal that further broadened at lower temperatures. The spectrum of the C-10 host **1c** (plus 0.5 equiv of Cl^-) at room temperature contained one very broad signal, but at −50 °C broad signals at +150 ppm (uncomplexed) and +40 ppm (1:1 complex) were observed. The spectrum

(1) For leading references to multidentate Lewis acid binding of anions and neutral donors see: Katz, H. E. *Organometallics* **1987**, *6*, 1134–1136. Austin, M.; Gebreyes, K.; Kuivila, H. G.; Swami, K.; Zubieta, J. A. *Ibid.* **1987**, *6*, 834–842. Wuest, J. D.; Zacharie, B. *J. Am. Chem. Soc.* **1987**, *109*, 4714–4715. Gielen, M.; Jurkschat, K.; Mahieu, B.; Apers, D. *J. Organomet. Chem.* **1985**, *286*, 145–151.

(2) Newcomb, M.; Madonik, A. M.; Blanda, M. T.; Judice, J. K. *Organometallics* **1987**, *6*, 145–150.

(3) Nicholson, J. W.; Douek, J. A.; Crowe, A. J. *J. Organomet. Chem.* **1981**, *219*, 309–316. Nadvornik, M.; Holecek, J.; Handlir, K.; Lycka, A. *Ibid.* **1984**, *275*, 43–51.

(4) Dietrich, B. In *Inclusion Compounds*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Eds.; Academic: London, 1984; Vol. 2, pp 337–405.

(5) Azuma, Y.; Newcomb, M. *Organometallics* **1984**, *3*, 9–14.

(6) Newcomb, M.; Blanda, M. T.; Azuma, Y.; Delord, T. J. *J. Chem. Soc., Chem. Commun.* **1984**, 1159–1160.

(7) ^{119}Sn NMR spectra of $CDCl_3$ solutions were recorded on Varian XL-200 (74.6 MHz) and XL-400 (149.2 MHz) spectrometers. Gated decoupling was used to suppress NOE. Chemical shifts were measured against internal Me_4Sn.

(8) Smith, P. J.; Tupciauskas, A. P. *Annu. Rep. NMR Spectrosc.* **1978**, *8*, 291–370. Petrosyan, V. S. *Prog. NMR Spectrosc.* **1977**, *11*, 115–148. Wrackmeyer, B. *Annu. Rep. NMR Spectrosc.* **1985**, *16*, 73–186.

0002-7863/87/1509-7878$01.50/0

Table I. Rate and Equilibrium Constants for Binding Chloride Ion by Hosts **1**[a]

host	temp (°C)	k_r (s^{-1})	k_f (M^{-1} s^{-1})[b]	K_{eq} (M^{-1})
1b[c]	−50	(2.0 ± 0.8) × 10^2	(9 ± 4) × 10^3	4_5
	−40	(3.6 ± 0.4) × 10^2	(2 ± 1) × 10^4	5_6
	−30	(8.4 ± 0.8) × 10^2	(3.7 ± 0.8) × 10^4	4_4
	−20	(2.0 ± 0.3) × 10^3	(7 ± 2) × 10^4	3_5
	−10	4 × 10^3	1 × 10^5	2_5
1c	−20	3 × 10^4	1 × 10^6	3_3
1d	−50	6 × 10^4	3 × 10^5	5
	−20	3 × 10^5	2 × 10^6	7
	20	3 × 10^6	1 × 10^7	3

[a] Results from line shape analyses of spectra of $CDCl_3$ solutions containing hosts and tetrahexylammonium chloride. Error limits, when given, are 1σ for multiple determinations and do not contain an estimate of systematic errors. Single determination values are given without error limits; these values are believed to be accurate to better than ±25% for k_r and ±50% for k_f. [b] k_f was calculated from the k_f' of the simulation and the concentration of free chloride. [c] Averages of four values for −50 to −30 °C and three values for −20 °C.

of the slower exchanging C-8 host **1b** (with 0.5 equiv of Cl^-) contained two sharp signals at −50 °C that broadened on warming (Figure 1).

$$\text{HOST} + Cl^- \underset{}{\overset{K_{eq}}{\rightleftharpoons}} (\text{HOST}\cdot Cl)^- \qquad (1)$$

The binding of chloride by **1b–d** is described by the simple model in eq 1. Line shape analyses of the spectra containing hosts **1b–d** and chloride gave kinetic results,[9] some of which are listed in Table I. The rates of complexation and decomplexation were slowed appreciably as the chain length decreased; we presume that this reflects steric interactions as the chloride squeezes between two chains to enter or exit the cavities. For host **1b**, studies of solutions of varying concentration indicated that decomplexation (k_r) was unaffected by concentration; an Arrhenius treatment for this first-order decomplexation of chloride from the $(\mathbf{1b}\cdot Cl)^-$ complex gave an E_a of 9.1 ± 0.5 kcal/mol (two solutions, 15 measurements between −50 and −20 °C, the error limit is 1σ). The binding constants of hosts **1b** and **1c** at −20 °C were substantially greater than that for host **1d**; apparently the best cavity size for chloride occurs between hosts **1b** and **1c**.

A more dramatic demonstration of size selectivity was found when the C-6 bicycle **1a** was studied. At room temperature the ^{119}Sn NMR spectrum of **1a** (+148 ppm) was unaltered by the addition of excess chloride. The absence of line broadening or a second signal in the +30 to +40 ppm region in the spectra of **1a** showed that no complexation occurred to the limit of our detection capabilities. With the conservative estimate that even in the most difficult to detect case (slow exchange limit) we would have observed 5% complex if it was present, we can set a limit on K_{eq} for **1a** of <1 M^{-1}. Host **1a** is not Lewis acidic toward chloride!

We have shown that highly selective anion binding in organic solvents is possible with appropriately constructed Lewis acidic hosts even when only two binding sites are available. The selectivity can result from either the exclusion of the guest from an under-sized cavity or the poor fit of the guest within an over-sized cavity. The replacement of chloride on bicycles **1** with a nonlabile electron-withdrawing group should be expected to give hosts that complex a variety of anionic and neutral basic guests selectively.

Acknowledgment. This work was supported by the Office of Naval Research.

(9) A two-site exchange model was used.[10] The T_2 values used in simulations were determined experimentally (Varian's CPMGT2 sequence) for host **1b** at 149.2 MHz (0.05 s for the uncomplexed and 0.003 s for the complexed signal).

(10) Sandström, J. *Dynamic NMR Spectroscopy*; Academic: London, 1982.

Assignment of ^{15}N NMR Signals in Bovine Pancreatic Trypsin Inhibitor

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Received June 26, 1987

With the development of ^1H detected heteronuclear chemical shift correlation spectroscopy, the detection of ^{15}N spectra has become possible for peptides and small proteins at natural abundance.[1,2] Recently, reports have shown that $^1H\{^{15}N\}$ correlation is feasible in small proteins,[3–5] though assignments were incomplete. The analysis of nitrogen chemical shifts of backbone and side chain amides for structural information[6,7] requires more extensive and accurate assignments. In addition, there has recently been considerable interest in studying ^{15}N enriched proteins,[8–10] and further improvements in understanding the origin of the variation of chemical shifts with primary, secondary, and tertiary structure are likely to be of general use. We have attempted a complete assignment of the $^1H\{^{15}N\}$ spectra from bovine pancreatic trypsin inhibitor (BPTI), a small (MW 6500) rigid protein which has been the molecule of choice for extensive proton NMR studies.[11,12] The chemical shifts of the backbone amides were then compared to model values, and the resulting differences analyzed with respect to amide hydrogen bonding, to torsional angles, and to other structural features available from the crystal structure and proton NMR studies. The general features of the X-ray crystal structure[13] are thought to be maintained in solution under a variety of temperatures and pH values.[14]

The assignments were derived first with data collected at 68 °C.[15] A phase-sensitive double-quantum-filtered COSY spectrum[16] at this temperature clarified regions of proton overlap and minor differences in proton chemical shifts from published values. A few peptide amide resonances and most carboxamide side chain resonances were not observed due to rapid proton exchange at 68 °C. Ambiguities arising from weak or absent signals and proton

(1) Bax, A.; Griffey, R. H.; Hawkins, B. L. *J. Magn. Reson.* **1983**, *55*, 301.
(2) Live, D. H.; Davis, D. G.; Agosta, W. C.; Cowburn, D. *J. Am. Chem. Soc.* **1984**, *106*, 6104–6105.
(3) Ortiz-Polo, G.; Krishnamoorthi, R.; Markley, J. L.; Live, D. H.; Davis, D. G.; Cowburn, D. *J. Magn. Reson.* **1986**, *68*, 303–310.
(4) Wagner, G. 27th ENC, Baltimore, MD, 1986.
(5) Sklenar,V.; Bax, A. *J. Mag. Reson.* **1987**, *71*, 379–383.
(6) Levy, G. C.; Lichter, R. L. In *Nitrogen-15 NMR Spectroscopy*, Wiley-Interscience: New York, 1979.
(7) Witanowski, M.; Stefaniak, L.; Webb, G. A. *Annu. Rep. NMR Spectrosc.* **1986**, *18*, 1–761.
(8) LeMaster, D. M.; Richards, F. M. *Biochemistry* **1985**, *24*, 7263–7268.
(9) Griffey, R. H.; Redfield, A. G.; Loomis, R. E.; Dahlquist, F. W. *Biochemistry* **1985**, *24*, 817–822.
(10) Schiksnis, R. A.; Bogusky, M. J.; Tsang, P.; Opella, S. J. *Biochemistry* **1987**, *26*, 2373–2382.
(11) Pardi, A.; Wagner, G.; Wüthrich, K. *Eur. J. Biochem.* **1983**, *138*, 445–454, and reference therein.
(12) Wagner, G.; Wüthrich, K. *J. Mol. Biol.* **1982**, *155*, 347–366.
(13) Deisenhofer, J.; Steigemann, W. *Acta Crystallogr., Ser. B: Struct. Crystallogr. Cryst. Chem.* **1975**, *B31*, 238–250. Wlodawer, A.; Walter, J.; Huber, R.; Sjölin, L. *J. Mol. Biol.* **1984**, *180*, 301–329.
(14) Wagner, G.; Braun, W.; Havel, T. F.; Schammann, T.; Gō, N.; Wüthrich, K. *J. Mol. Biol.* **1987**, *196*, 611–639.
(15) As was discussed in a recent paper (ref 5), the experiment of choice for ^{15}N in water omits the refocusing 180° ^1H pulse but includes hetero-decoupling during acquisition. The authors collected multiquantum ^1H decoupled correlated data in separate blocks, processed them separately, and added the resulting spectra. Though these procedures considerably improve signal-to-noise under favorable conditions, resolution and information can be lost. In the data analyzed here, the limiting factors were the proton spectral overlap and the wide range in intensity of the nitrogen signals. Therefore, we collected only multiquantum coupled data and analyzed the spectra separately. The pattern of doublets with both $^1J(^{15}N-^1H)$ and $^3J(^1H-^1H)$ allowed differentiation between true signals and noise and thus compensated for the apparent increase in complexity.
(16) Rance, M.; Sørensen, O. W.; Bodenhausen, G.; Wagner, G.; Ernst, R. R.; Wüthrich, K. *Biochem. Biophys. Res. Commun.* **1983**, *117*, 479–485.

0002-7863/87/1509-7879$01.50/0