(bp 60–80 °C)) and were further purified by trap-to-trap distillation under reduced pressure. 2-(*tert*-Butylperoxy)-3-iodopentanes I2A and I2B were similarly obtained from M2.

For I1A (23% yield): ^{1}H NMR (60 MHz) ppm 1.00 (t, 3 H, ^{5}CH$_3$), 1.2–2.0 (m, 2 H, ^{4}CH$_2$), 1.20 (s, 9 H, *t*-Bu), 1.76 (d, *J* = 7 Hz, 3 H, ^{1}CH$_3$), 3.86 (dt, *J* = 7 and 4 Hz, 1 H, ^{3}CHO), and 4.57 (dq, *J* = 7 and 4 Hz, 1 H, ^{2}CHI).

For I1B (33% yield): ^{1}H NMR (60 MHz) ppm 1.00 (t, 3 H, ^{5}CH$_3$), 1.25 (s, 9 H, *t*-Bu), 1.3–1.9 (m, 2 H, ^{4}CH$_2$), 1.88 (d, *J* = 7 Hz, 3 H, ^{1}CH$_3$), 3.17 (dt, *J* = 7 and 4 Hz, 1 H, ^{3}CHO), and 4.61 (dq, *J* = 7 and 4 Hz, 1 H, ^{2}CHI).

For I2A (20% yield): ^{1}H NMR (60 MHz) ppm 1.04 (t, 3 H, ^{5}CH$_3$), 1.20 (s, 9 H, *t*-Bu), 1.23 (d, *J* = 7 Hz, 3 H, ^{1}CH$_3$), 1.4–2.0 (m, 2 H, ^{4}CH$_2$), and 3.97–4.47 (m, 2 H, ^{2}CHO and ^{3}CHI).

For I2B (25% yield): ^{1}H NMR (200 MHz) ppm 1.07 (t, *J* = 3 Hz, 3 H, ^{5}CH$_3$), 1.21 (d, *J* = 6 Hz, 3 H, ^{1}CH$_3$), 1.5–2.0 (m, 2 H, ^{4}CH$_2$), 1.27 (s, 9 H, *t*-Bu), 3.43 (dq, *J* = 6 and 4 Hz, 1 H, ^{2}CHO), and 4.40 (dt, *J* = 6 and 4 Hz, 1 H, ^{3}CHI); all ^{13}C NMR data are given in Table I.

For a mixture of I1A, I1B, I2A, and I2B: Anal. Calcd for C$_9$H$_{19}$IO$_2$: C, 37.77; H, 6.69. Found: C, 37.52; H, 6.73.

Reaction of β-Iodopentyl *tert*-Butyl Peroxides with Silver Trifluoroacetate. Silver trifluoroacetate (86 mg, 0.30 mmol) was added to a solution of the β-iodopentyl *tert*-butyl peroxide (100 mg, 0.35 mmol) in methylene chloride (50 mL) at reflux, and the mixture was stirred for 1 h. The mixture was then filtered through a sintered glass funnel (5-cm diameter) containing silica gel (0.5 cm) covered with Celite (0.2 cm). The methylene chloride was removed under vacuum to afford the β-(trifluoroacetoxy)-pentyl *tert*-butyl peroxide(s) (T).

For T1 + T2 (yield from I1A, 59 mg, 0.22 mmol, 62%; yield from I2A, 51 mg, 0.19 mmol, 54%): ^{1}H NMR (60 MHz) ppm 0.8–1.9 (m, 8 H, ^{5}CH$_3$, ^{4}CH$_2$, and ^{1}CH$_3$), 1.22 (s, 9 H, *t*-Bu), 3.8–4.3 (m, 1 H, ^{3}CHOO of T1 and ^{2}CHOO of T2), and 5.0–5.6 (m, 1 H, ^{2}CHO$_2$CCF$_3$ of T1 and ^{3}CHO$_2$CCF$_3$ of T2); IR (C=O) 1779 cm^{-1}.

For T3 (yield from I1B, 60 mg, 0.22 mmol, 63%): 0.8–1.9 (m, 5 H, ^{5}CH$_3$ and ^{4}CH$_2$), 1.22 (s, 9 H, *t*-Bu), 1.33 (d, *J* = 7 Hz, 3 H, ^{1}CH$_3$), 3.87 (dt, *J* = 7 and 3 Hz, 1 H, ^{3}CHOO), and 5.40 (dq, *J* = 7 and 3 Hz, 1 H, ^{2}CHO$_2$CCF$_3$); IR (C=O) 1779 cm^{-1}.

For T4 (yield from I2B, 55 mg, 0.20 mmol, 58%): 0.8–1.9 (m,

8 H, ^{5}CH$_3$, ^{4}CH$_2$, and ^{1}CH$_3$), 1.22 (s, 9 H, *t*-Bu), 4.16 (dq, *J* = 7 and 3 Hz, 1 H, ^{2}CHOO), and 5.30 (dt, *J* = 7 and 3 Hz, 1 H, ^{3}CHO$_2$CCF$_3$); IR (C=O) 1782 cm^{-1}; all ^{13}C NMR data are given in Table I.

For a mixture of T1, T2, T3, and T4, purified by medium pressure chromatography (50 cm × 2.25 cm, silica gel, 1% EtOAc in light petroleum ether (bp 60–80 °C)) followed by trap-to-trap distillation under reduced pressure: Anal. Calcd for C$_{11}$H$_{19}$F$_3$O$_4$: C, 48.52; H, 7.03. Found: C, 48.32; H, 6.95.

Preparation of β-Bromopentyl *tert*-Butyl Peroxides B1A and B2A. A mixture of M1 and M2 was treated with bromine and sodium bromide in methanol[10] to afford a mixture of bromo peroxides B1A and B2A: ^{1}H NMR (60 MHz) ppm 0.7–2.1 (m, 8 H), 1.22 (s, 9 H), and 3.8–4.6 (m, 2 H).

Preparation of β-Bromopentyl *tert*-Butyl Peroxides B1B and B2B. Peroxymercuration of (*E*)-pent-2-ene using the procedure previously described[10] afforded a mixture of M3 and M4: ^{1}H NMR (60 MHz) ppm 0.9–2.1 (m, 8 H), 1.30 (s, 9 H), 2.8–3.2 (m, 1 H), and 4.0–4.6 (m, 1 H). Brominolysis as described above gave a 2:1 mixture of B1B + B2B and B1A + B2A: ^{1}H NMR (60 MHz) ppm 0.7–2.2 (m, 8 H), 1.25 (s, 9 H), and 3.5–4.6 (m, 2 H).

Reduction of T1 and T2. A solution of T1 + T2 (0.93 g, 3.4 mmol) in diethyl ether (50 mL) was added during 1 h to a vigorously stirred suspension of LiAlH$_4$ (0.30 g, 7.9 mmol) in diethyl ether (25 mL) at reflux, and the mixture was kept at reflux for a further 1 h. Ethyl acetate (2.0 g) was then added dropwise to destroy unreacted LiAlH$_4$. After 15 min, the mixture was allowed to cool, and water (0.30 mL), then 15% aqueous NaOH (0.30 mL), and then water (0.90 mL) were added dropwise. The mixture was filtered through Celite and shaken with brine (50 mL), and the organic layer was isolated. The aqueous layer was extracted with diethyl ether (2 × 50 mL). The organic phases were combined and dried (MgSO$_4$), and the solvent was removed under reduced pressure to afford an oil (0.19 g, 1.8 mmol, 54%) with spectroscopic characteristics identical with those of authentic *threo*-pentane-2,3-diol: ^{1}H NMR (60 MHz) ppm 0.7–1.8 (m, 8 H), and 3.0–4.2 (m, 4 H); ^{13}C NMR ppm 9.93, 19.50, 26.20, 70.57, and 77.56.

Cation Binding Properties and Molecular Structure of the Crystalline Complex (Aza-12-crown-4)$_2$•NaI

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Aza-12-crown-4 forms a 2:1 sandwich complex similar to that known for 12-crown-4 sodium iodide, except that the presence of >NH in each ring makes Na–donor bonds unequal in strength and leads to hydrogen bonding with the counterion. The heteroatoms of each macroring are coplanar, and both nitrogens are on the same side of the complex (twist angle 43° from eclipsed). This may be due to a long (and weak) hydrogen bond to iodide, an interaction confirmed by analysis using Raman spectroscopy. The previously unreported 1:1 and 2:1 cation affinity constants (anhydrous MeOH, 25 °C) for this macrocycle are log $K_{S(1:1)}$ = 1.3 ± 0.1 and log $K_{S(2:1)}$ = 2.0 ± 0.1, respectively.

The recognition that naturally occurring macrocyclic ionophores such as valinomycin,[1] enniatin,[2] and beauvericin[3] all form three-dimensional complexes with cations has renewed interest in small-ring systems. When two small

macrorings are present in the same molecular array, they can cooperate to form intramolecular sandwich complexes

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in which the donor groups fully encompass the bound species.[4] This possibility has been apparent from the first crystal structure, reported by van Remoortere and collaborators,[5] of [(12-crown-4)₂·Na]⁺ and has been confirmed more recently for the analogous sandwich complexes of Ag, Cu, Li, and Fe cations.[6] In more recent work, macrocycles have been joined by various tethers to make pre-sandwich systems, which are partially organized. Notable among the latter work is the report by Calverley and Dale[7] of a synthetic method for the preparation of aza-12-crown-4 (1), an excellent, functionalized precursor to such systems.

In our own recent work, we have prepared a number of N-substituted aza-12-crown-4 derivatives having donor groups present in the sidearms.[8] We have recently demonstrated that when six oxygen donor groups are present in the molecular array, very stable complexes can be formed even with cations that seem to be "too large" for the macroring.[9] It occurred to us that an especially stable complex might form between Na⁺ and aza-12-crown-4. Molecular models (framework and CPK) suggested that such a complex might have a structure in which the six oxygen donor groups formed an octahedral array about Na⁺ and the >NH residues stabilized the complex by hydrogen bonding. We therefore undertook the study reported here in which we examined the complex between 1 and Na⁺ in solution and the solid state.

Results and Discussion

Syntheses. Aza-12-crown-4 (1) was prepared from *N*-benzylaza-12-crown-4 as reported by Calverley and Dale[7] based on the procedure we developed some years ago.[10]

PhCH₂NH₂ + I(CH₂CH₂O)₂CH₂CH₂I ⟶

PhCH₂N⟨⟩O, O → $\xrightarrow[\text{Pd-C}]{\text{H}_2}$ → HN⟨⟩O, O

1
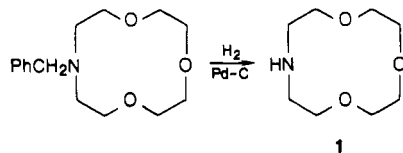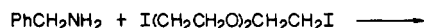
The 2:1 complex was prepared by stirring together 1 and NaI in 1,2-dichloroethane solution and recrystallizing the crude solid complex from THF. Pure 1₂·NaI was obtained as a white solid, mp 180–182 °C.

Cation Binding Studies. Cation complexation or stability constants offer a method for learning about cation–macrocycle interactions in solution. Comparison of
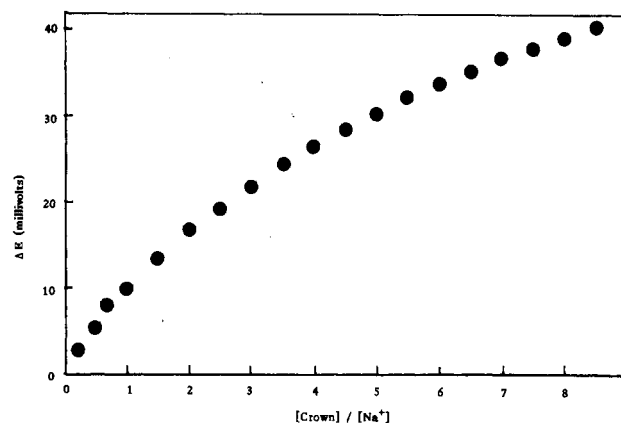

Figure 1. Titration curve for aza-12-crown-4 with NaCl in anhydrous methanol at 25.0 ± 0.1 °C.
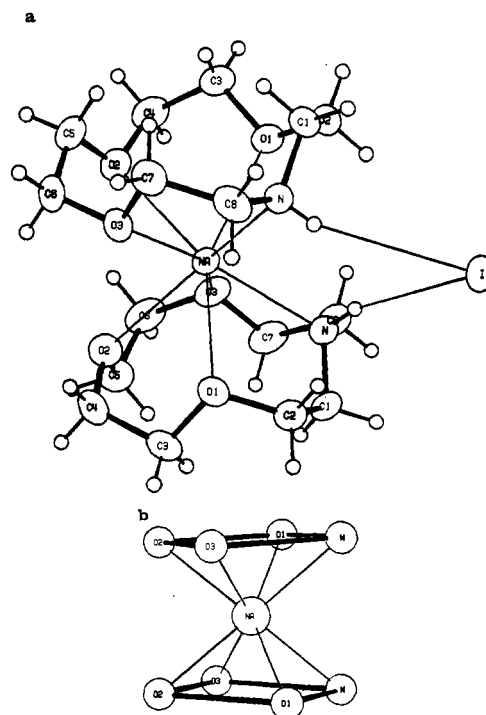

Figure 2. X-ray crystal structure of (aza-12-crown-4)₂·NaI (a) showing all atoms and (b) showing only Na⁺ and the donor groups.

measurements on new macrocyclic systems with the extensive compilations recorded by Izatt et al.[11] permits one to assess the effects of geometry, donor group number and identity, and other factors. The stability constants reported here are for homogeneous solutions of anhydrous methanol at 25 ± 0.1 °C. Values were determined by ion-selective-electrode (ISE) techniques as described in the Experimental Section and previously.[12]

The cation binding ability of 1 with Na⁺ was reported by Dale.[7] The experiment involved addition of Na⁺ in CH₃OD to an excess of 1, 0.5 M in CH₃OD. A titration curve was obtained by ¹³C NMR spectroscopy, but no values for K_S were reported for either the 1:1 or 1:2 complexation reactions. Michaux and Reisse.[13] Hoiland et al.,[14] and Miyazaki et al.[15] have all reported stability con-

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Table I. Selected Bond Distances, Bond Angles, and Torsion Angles for (Aza-12-crown-4)$_2$·NaI

atoms	distance, Å	atoms	angle, deg
Na–N	2.534 (2)	N–Na–O1	67.82 (6)
Na–O1	2.626 (2)	N–Na–O2	104.06 (7)
Na–O2	2.545 (2)	N–Na–O3	69.19 (6)
Na–O3	2.470 (2)	N–Na–N′	86.92 (10)
N–C1	1.451 (3)	N–Na–O1′	90.23 (6)
N–C8	1.457 (3)	N–Na–O2′	146.36 (7)
O1–C2	1.422 (3)	N–Na–O3′	143.50 (7)
O1–C3	1.422 (3)	O1–Na–O2	65.98 (6)
N–H1N	0.76 (2)	Ou–Na–O3	104.73 (6)
C1–C2	1.505 (3)	O1–Na–O1′	150.18 (7)
C3–C4	1.496 (5)	C2–O1–C3	113.9 (3)
C5–C6	1.498 (6)	C4–O2–C5	114.5 (3)
C7–C8	1.507 (4)	C1–N–C8	115.0 (3)
C–H range	0.90 (3)–1.09 (5)	N–C1–C2	110.3 (2)
		C1–C2–O1	112.5 (2)
		N–C1–C2–O1	59.8
		C1–C2–O1–C3	80.2
		C2–O1–C3–C4	−162.9
		O1–C3–C4–O2	59.6
		C3–C4–O2–C5	79.0
		C4–O2–C5–C6	−165.1
		O2–C5–C6–O3	60.7
		C5–C6–O3–C7	77.8
		C6–O3–C7–C8	−163.8
		O3–C7–C8–N	60.2
		C7–C8–N–C1	78.1
		C8–N–C1–C2	−162.2

Table II. Comparison of Structural Features in Sodium Sandwich Complexes of 12-Crown-4 and Aza-12-crown-4

	12-crown-4			aza-12-crown-4, NaI^d
	NaOH·H$_2$O^a	NaClO$_4$^{b}	NaCl·5H$_2$O^c	
Na–O, Å	2.441	2.475	2.473	2.470
	2.459	2.474	2.488	2.545
	2.483	2.478	2.508	2.626
	2.489	2.483	2.517	
	2.491	2.488		
	2.493	2.492		
	2.508	2.542		
	2.514	2.525		
Na–N, Å				2.534
cavity size, Å	1.085	1.09	1.096	1.119
distance from best donor plane	1.497	1.505	1.53	1.528
	1.505			

^{a} See ref 5b. ^{b} See ref 5c. ^{c} See ref 5a. ^{d} This work.

stants for the reaction of 12-crown-4, the all-oxygen parent of 1, with Na$^+$. The value of log K_S for 1:1 complexation is 1.41–1.47, and for 2:1 complexation it is 2.20–2.29. Details of the calculations used may be found in the Experimental Section.

The plot of our cation binding data is shown in Figure 1. From the titration curve, we were able to assign the following cation stability constants to the interaction of Na$^+$ with 1: log $K_{S(1:1)}$ = 1.3 ± 0.1 and log $K_{S(2:1)}$ = 2.0 ± 0.1. Note that the error limits refer to the precision of our data. We cannot be certain about the accuracy of these values, but we estimate the error to be <15% on the basis of our extensive experience with cation binding constants in related systems. The similarity in K_S values for 12-crown-4 and aza-12-crown-4 is striking and suggests that the oxygen donor groups dominate the cation binding. For comparison, we note that log K_S values obtained for Na$^+$ (MeOH, 25 °C) with 15-crown-5 and N-butylaza-15-crown-5 were 3.24 (1737) and 3.02 (1047), respectively.

Description of Structure. In order to determine precisely what interaction(s) between 1 and Na$^+$ occurred, we analyzed the complex by X-ray crystallographic and Raman spectroscopic techniques. The structure of (aza-12-crown-4)$_2$·NaI is illustrated in Figure 2, in which the sandwich configuration is evident. The complex has crystallographic C_2 symmetry. Each macroring is in the crown conformation [(g$^+$g$^+$a)$_4$], in which all heteroatoms are on the same side of the ring. The four heteroatoms of each aza-12-crown-4 are coplanar to within 0.003 (2) Å, and the Na$^+$ ion lies 1.557 Å from the centroid of the four. Sodium–heteroatom distances are as follows: N, 2.534 (2) Å; O1, 2.626 (2) Å; O2, 2.545 (2) Å; and O3, 2.470 (2) Å. The two heteroatom least-squares planes that sandwich the cation are not quite parallel, forming a dihedral angle of 3.7°. The eight donors form an approximate square antiprism around the cation, as seen in the skeletal drawing, Figure 2b. Whereas, in an ideal square antiprism, the N–centroid–centroid′–N′ torsion angle would be 45°, this

twist angle is actually 43.3°. Both N atoms are thus on the same side of the molecule, and both form N–H···I contacts to a single iodide ion. The anion is 5.316 (1) Å distant from Na$^+$ in this ion pair. The N···I distances are 3.729 (2) Å, H···I distances are 3.02 (2) Å, and N–H···I angles are 157 (3)°. These contacts may be considered to be weak hydrogen bonds. A selected set of bond distances (in angstroms), angles, and torsion angles is shown in Table I.

A comparison of structural features of various 12-crown-4 complexes of sodium cation with the aza-12-crown-4 complex is presented in Table II. All complexes have a square-antiprism arrangement of donor atoms around the sodium cation. The aza-12-crown-4 complex has the two rings of donors farther apart than observed for 12-crown-4 complexes. This is expected since the nitrogen covalent radius is larger than that of oxygen. The Na–N distance is short when compared to other macrocyclic complexes.[16] The cavity sizes for all the sandwich complexes are considerably smaller than the 1.18 Å expected from Shannon's value[17] for eight-coordinated sodium cation.

Raman Spectroscopic Analysis. Raman spectroscopy provides considerable insight into the hydrogen bonding and weak electrostatic interactions that stabilize the (aza-12-crown-4)$_2$·NaI complex. Raman spectra were obtained for the crystalline complex, the complex dissolved in (CH$_2$Cl)$_2$, the free crown, and the free crown dissolved in (CH$_2$Cl)$_2$. The spectra of the complex in (CH$_2$Cl)$_2$ and the crystalline complex are shown in Figure 3.

While for this work the high-frequency region is of greatest interest, a few general features of the 200–1650-cm^{-1} spectra should be noted. The spectra for the dissolved and crystalline complex in the 200–1650-cm^{-1} region are quite similar. (Note that only the major peaks and the principal peaks of closely spaced multiplets have been marked in Figure 3.) There is some broadening of peaks in the solution spectrum, and small (ca. 2–3 cm^{-1}) shifts are observed relative to bands at 1031, 1144, 1264, 1436, and 1488 cm^{-1} in the crystalline complex. The apparent shifts in the 1400–1500-cm^{-1} region may actually result from overlap of solvent vibrational modes with those of the complex. The C–H stretching region for the complex in solution is not shown, since the solvent bands obscure those of the complex.

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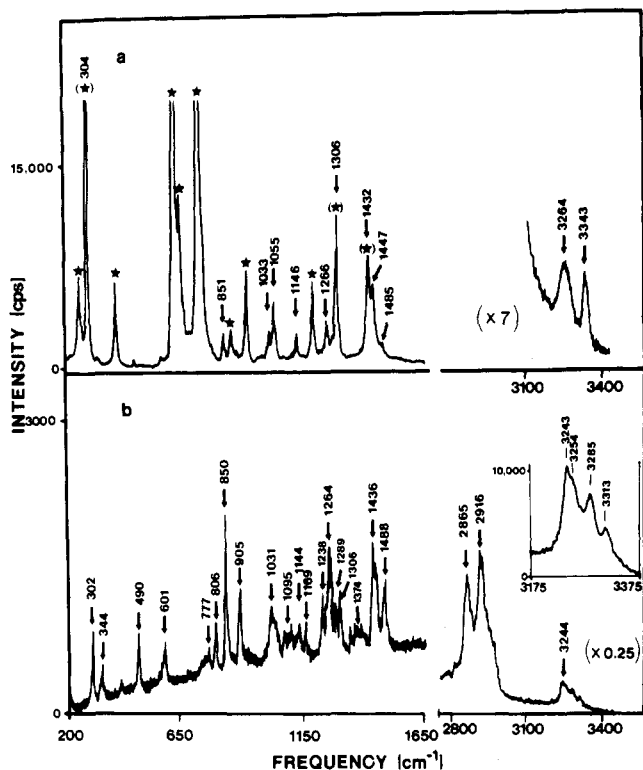
Figure 3. Raman spectra of (aza-12-crown-4)₂·NaI complex. (a) In dichloroethane solution. (Conditions: 20-mW 5145-Å laser irradiation, 200–240-inf-200 μm slitwidths. 200–1650-cm⁻¹ region: four scans, each 2 s per 1 cm⁻¹ step. High-frequency region: six scans, each 2 s per 1 cm⁻¹ step.) (b) As the crystalline complex. (Conditions: 40-mW 5145-Å laser irradiation, 70–90–90–70 μm slitwidths. 200–1620-cm⁻¹ region: one scan, 1 s per 0.5 cm⁻¹ step. 2750–3450-cm⁻¹ region: two scans, each 1 s per 1-cm⁻¹ step. Inset: 100–120–120–100 μm slitwidths, seven scans, each 1 s per 1 cm⁻¹ step.)

Table III. N–H Stretching Frequencies (Raman, in cm⁻¹) for (Aza-12-crown-4)₂•NaI and Aza-12-crown-4

crystalline crown complex	complex in (CH₂Cl)₂	crystalline free crown	free crown in (CH₂Cl)₂
3243			
3254 (sh)	3264		
3285		3307 not	
		3314 resolved	
3313	3343		3322

The complexed crown has higher symmetry than the uncomplexed crown, as evidenced by the smaller number and greater intensity of Raman active vibrational modes. This suggests that the conformation of the uncomplexed crown is C_1. The spectral changes are consistent with those observed for 18-crown-6 and its complexes with potassium salts[18] and neutral molecules.[19]

The N–H stretching vibration is extraordinarily sensitive to subtle changes in molecular structure, crystalline packing forces, and solvent interactions. Table III lists the N–H stretching frequencies observed for the crown complex and the free complex, both in the crystalline form and dissolved in (CH₂Cl)₂. The spectrum of the free crown in solution shows a single N–H stretching vibration at 3322

cm⁻¹. This value is well within the frequency range 3200–3350 cm⁻¹ characteristic of aliphatic secondary amines.[20] Weak intermolecular hydrogen bonding with the solvent may be present. In the crystalline, uncomplexed crown, the N–H stretching vibration shifts slightly and splits into two (unresolved) bands at 3307 cm⁻¹ and 3314 cm⁻¹. This splitting is most likely due to crystal packing forces or to very small differences in site symmetry.[21] We do not expect to observe coupling between the N–H modes of proximal crown molecules in the uncomplexed crystal, since there are no intervening cations to mediate the interaction.

The 2:1 crown·NaI complex in solution shows two different >N–H stretching vibrations, at 3264 cm⁻¹ and 3343 cm⁻¹. Since the Raman spectra of the crystalline and dissolved complexes in the 200–1650-cm⁻¹ region are quite similar, it is likely that the symmetry of the complex is the same in the two environments. The diffraction data show that the two H···I distances and >N–H···I angles in the complex are nearly identical. The two >N–H stretching frequencies observed for the complex in solution are therefore probably attributable to the in-phase and out-of-phase vibrations of the >N–H bonds. The frequency shifts +21 and −48 cm⁻¹ relative to the frequency observed for the free crown in solution are consistent with this hypothesis. It is particularly interesting that the >N–H stretching modes are coupled, considering that there are no covalent attachments between the macrocycles. The rings are held together primarily through interactions with the central sodium cation and the more remote iodide. There may, however, exist additional dipolar interactions that serve to couple the vibrations of the two macrocycles and enhance the stability of the complex. For example, the inter-ring O1···H(N) distance is 3.52 Å compared with the (N)H···I distance of 3.02 Å. Although 3.5 Å is too great a distance and the geometry incorrect for the O1···H(N) interaction to be considered true hydrogen bonding, significant electrostatic interactions probably occur and contribute to the stability of the complex.

The Raman spectrum of the crystalline complex shows four bands, three of which are well-resolved (3243, 3285, and 3313 cm⁻¹) and the fourth of which appears as a distinct shoulder (3254 cm⁻¹). The spectrum is far more complex than one might have predicted from the symmetry of the complex and the unit cell. Note that there are four >NH groups per unit cell: two in each complex and two complexes in each unit cell. We interpret the four Raman bands as resulting from the two modes (in-phase and out-of-phase) for the single complex vibrating in-phase and out-of-phase with those of the second complex in the unit cell. The frequencies are perturbed by weak dipolar interactions between the complexes. These interactions include those between the amine hydrogen and the nearest oxygen on an adjacent complex, the distance between which is on the order of 4.5 Å. Vibrational spectroscopic studies of related azacrowns should provide additional insight and are currently underway.

Summary

Aza-12-crown-4 readily forms a 2:1 sandwich complex with NaI. Its solid-state structure is similar to the sandwich structure adopted by 12-crown-4 except that the two >N–H bonds are separated by only 43.3° and exhibit a weak interaction with the iodide ion. This interaction is

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clearly electrostatic and may be interpreted as a weak hydrogen bond. Equilibrium cation binding studies using ion-selective-electrode techniques suggest that 2:1 complexes form in anhydrous methanol solution, and the magnitudes of their equilibrium stability constants are quite similar to those of the parent, 12-crown-4. Raman spectroscopy confirms the sandwich structure in dichloroethane solution.

Experimental Section

Melting points (Thomas-Hoover apparatus, open capillaries) are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 281 spectrophotometer as neat samples unless otherwise noted. Spectral bands are reported in cm^{-1} and calibrated against the 1601-cm^{-1} band of polystyrene. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded at 60 MHz as ca. 15 wt. % solutions in $CDCl_3$ unless otherwise specified. Chemical shifts in parts per million (δ) downfield from internal Me_4Si are reported in the following order: chemical shift, spin multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), and integration. Combustion analyses (C, H, N) were performed by Atlantic Microlab, Atlanta, GA.

All reagents were the best grade commercially available and were used without further purification unless otherwise specified. Tetrahydrofuran (THF) was distilled from $LiAlH_4$ or Na-benzophenone under a dry N_2 atmosphere immediately before use. Oven temperatures are given for bulb-to-bulb distillations conducted in a Kugelrohr apparatus. Preparative chromatography columns were packed with MCB activated Al_2O_3 (80-325 mesh, chromatographic grade, AX-611) or Fluka silica gel 60 (70-230 mesh, chromatographic grade). Precoated sheets (aluminum oxide 60 F-254 neutral-Type E or silica gel 60 F-254), 0.2-mm thick, were used for TLC analyses.

N-Benzylaza-12-crown-4 was prepared according to the procedure of Calverley and Dale.[7] A stirred solution of 1,11-diiodo-3,6,9-trioxaundecane (4.3 g, 0.01 mol) and benzylamine (0.011 mol) in MeCN (150 mL) containing anhydrous Na_2CO_3 (5.3 g, 0.05 mol) was heated to reflux under an atmosphere of N_2 for 18 h. The mixture was then allowed to cool and was filtered. The filtrate was concentrated. The residue was stirred in CH_2Cl_2 (150 mL) and filtered to remove the residual salts. The solvent was removed in vacuo. The pure product was obtained (54%) as a colorless oil after chromatography (Al_2O_3) and molecular distillation (bp 122-125 °C (0.05 torr)).

Aza-12-crown-4 (1) was prepared by hydrogenolysis of N-benzylaza-12-crown-4 in 95% yield[10] and had properties identical with those reported.[8] ^1H NMR: 1.88 (s, 1 H), 2.73 (t, 4 H), 3.63 (m, 12 H) ppm.

Preparation of (Aza-12-crown-4)$_2$·NaI. To a solution of aza-12-crown-4 (2 equiv) and $ClCH_2CH_2Cl$ was added NaI (1.05 equiv). The mixture was stirred at room temperature for 1 h and filtered, and the volatiles were evaporated in vacuo. The resulting white solid was recrystallized from tetrahydrofuran (25 mg/mL) and the complex obtained (80%) as a white powder, mp 180-182 °C. ^1H NMR ($CDCl_3$): 2.15 (s, 1 H), 2.80 (t, 4 H), 3.63 (m, 12 H). IR (Nujol): 3240, 2840, 1280, 1260, 1235, 1130, 1090, 1030, 920, 840 cm^{-1}. Anal. Calcd for $C_{16}H_{34}N_2O_6$·NaI: C, 38.40; H, 6.86; N, 5.60. Found: C, 38.62; H, 7.10; N, 5.94.

Stability Constant Measurements. The equilibrium stability constants (log K_S) for the reaction $1 + NaCl$ = complex were determined in absolute methanol at 25.0 ± 0.1 °C by using ion-selective-electrode techniques as recently described.[22] Aza-12-crown-4 (4.969 mM) was added in 1-mL increments to 10 mL of 1.998 mM $NaClO_4$ up to 35 mL total volume. Values for binding constants were calculated as described below.

Calculations. The stability constants for a 1:1 crown-to-metal complex and a 2:1 (crown)$_2$metal complex are defined as follows:

$$K_S^1 = [MCr^+]/[M^+]_{free}[Cr]_{free}$$

$$K_S^2 = [MCr_2^+]/[MCr^+][Cr]_{free}$$

assuming activity coefficients of 1. $[M^+]_{free}$ was calculated at each point (n) on the curve by using the Nernst equation.

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$$\Delta E = E_{initial(volts)} - E_{point\ n(volts)}$$

$$[M^+]_{free,point\ n} = [M^+]_{initial} \times 10^{-\Delta E/0.0591}$$

The $[M^+]_{total}$ was calculated at each point (n).

$$[M^+]_{total} = ([M^+]_{initial})(initial\ volume)/(total\ volume)$$

The ratio $K_S^1/K_S^2 = [MCr^+]^2/([M^+]_{free}([MCr_2^+])$. The mass balance equation for metal was used to solve for $[MCr_2^+]$, and the value was substituted into the previous equation.

$$[MCr_2^+] = [M^+]_{total} - [M^+]_{free} - [MCr^+]$$

$$K_S^1/K_S^2 = [MCr^+]^2/([M^+]_{free}([M^+]_{total} - [M^+]_{free} - [MCr^+])$$

Assuming a value for K_S^1/K_S^2 and substituting the values for $[M^+]_{free}$ and $[M^+]_{total}$, the quadratic equation was used to solve for $[MCr^+]$.

$$[MCr^+]^2 + [M^+]_{free}(K_S^1/K_S^2)[MCr^+] - \langle(K_S^1/K_S^2)[M^+]_{free})([M]_{total} - [M^+]_{free}^2) = 0$$

The value of $[MCr^+]$ calculated was substituted into the mass balance equation for metal, which was solved for $[MCr_2^+]$.

$$[MCr_2^+] = [M^+]_{total} - [M^+]_{free} - [MCr^+]$$

Total crown concentration, $[Cr]_{total}$, was calculated at each point (n).

$$[Cr]_{total} = ([Cr])(volume\ added)/(total\ volume)$$

The mass balance expression was used to solve for $[Cr]_{free}$.

$$[Cr]_{free} = [Cr]_{total} - [MCr^+] - 2[MCr_2^+]$$

The value of K_S^1 was calculated by using the values of $[M^+]_{free}$, $[Cr]_{free}$, and $[MCr^+]$, and K_S^2 was determined by using the values of $[MCr^+]$, $[Cr]_{free}$, and $[MCr_2^+]$. A value for K_S^1 and K_S^2 was obtained for each data point. The values were averaged, and a standard deviation was calculated. Iteration of the K_S^1/K_S^2 was continued until the smallest standard deviation was reached.

Raman Spectroscopy. Raman spectra were recorded on a spectrometer comprising of a Cooper Lasersonics Aurora argon laser operated at 514.4 nm, Spex 1403 double monochromator equipped with 1800 groove/mm holographic gratings, RCA C31034-04 cooled photomultiplier, and Spex Lab Controller data acquisition and storage system. Each spectrum was smoothed with a five-point polynomial smoothing function and the background subtracted with a horizontal base-line subtraction routine.

X-ray Crystallographic Studies. A square-pyramidal crystal of dimensions 0.48 × 0.48 × 0.50 mm was used for data collection on an Enraf-Nonius CAD4 diffractometer equipped with Mo $K\alpha$ radiation (λ = 0.71073 Å) and a graphite monochromator. Lattice parameters and crystal orientation were determined from a least-squares fit of setting angles of 25 reflections having 13° < θ < 14°. Crystal data and details of data collection are as follows. Formula: $(C_8H_{17}NO_3)_2NaI$. Molecular weight: 500.4. Space group: tetragonal, $P4_32_12$. a: 10.159 (1) Å. c: 22.518 (3) Å. V: 2324.0 (8) Å^3. Z: 4. D_{calcd}: 1.430 g cm^{-3}. μ: 14.1 cm^{-1}. Scan rates: 0.45-4.0 deg min^{-1}. θ limits: 1-30°. Unique data: 3382. Observed data [$I > 3\sigma(I)$]: 2566. Variables: 188. R= 0.026. R (all data): 0.052. R_w: 0.029. GOF: 1.465. Maximum residual density (e Å^{-3}): 0.82. Extinction coefficient: 3.4 (2) × 10^{-7}.

Systematic absences indicated space group $P4_12_12$ or its enantiomorphous $P4_32_12$; the latter was proved by successful refinement with anomalous scattering factors. One octant of data within the specified θ limits was collected by $\omega - 2\theta$ scans designed for $I = 50\sigma(I)$, at 24 °C. Data reduction included corrections for background, Lorentz, polarization, decay (11%), and absorption (minimum relative transmission 94.37% by ψ scans).

The structure was solved by heavy-atom methods using the Enraf-Nonius SDP programs.[24] Atomic scattering factors of Cromer and Waber[25] and anomalous coefficients of Cromer[26] were

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(26) Cromer, D. T. *International Tables for X-Ray Crystallography*; Kynoch: Birmingham, England, 1974; Vol. IV, Table 2.3.1.

Table IV. Coordinates for (Aza-12-crown-4)$_2$•NaI

atom	x	y	z
I	0.79062 (1)	x	0
Na	0.43313 (8)	x	0
O1	0.3036 (1)	0.6568 (2)	0.00259 (8)
O2	0.1935 (2)	0.4104 (2)	0.03122 (10)
O3	0.4148 (2)	0.3453 (2)	0.10192 (8)
N	0.5290 (2)	0.5933 (2)	0.07463 (9)
C1	0.4493 (3)	0.7095 (3)	0.0850 (1)
C2	0.3864 (3)	0.7545 (2)	0.0280 (1)
C3	0.1767 (3)	0.6493 (3)	0.0291 (2)
C4	0.1170 (3)	0.5200 (4)	0.0121 (2)
C5	0.1784 (3)	0.3779 (4)	0.0921 (2)
C6	0.2882 (4)	0.2872 (3)	0.1093 (1)
C7	0.4478 (4)	0.4345 (3)	0.1480 (1)
C8	0.5618 (3)	0.5182 (3)	0.1277 (1)

used. Refinement was carried out by full-matrix least squares based on F with weights $w = \sigma^{-2}(F\sigma)$, treating non-hydrogen atoms anisotropically. Hydrogen atoms were located by difference maps and refined isotropically. Convergence was obtained (Δ/ρ maximum = 0.04) in $P4_32_12$ with agreement factors listed above. Seven

reflections had ΔF greater than $5\sigma(F)$, none greater than $7\sigma(F)$. Refinement under identical conditions in $P4_12_12$ yielded $R = 0.033$, $R_w = 0.038$, GOF = 1.926, 51 reflections with $\Delta F > 5\sigma(F)$, and five reflections with $\Delta F > 8\sigma(F)$. The difference in R_w is significant at better than $\alpha = 0.005$ by the Hamilton R factor ratio test.[27] Coordinates for the correct configuration are listed in Table IV.

Supplementary Material Available: Anisotropic thermal parameters for ($C_8H_{17}NO_3$)$_2$•NaI, coordinates and isotropic thermal parameters for hydrogen atoms of ($C_8H_{17}NO_3$)$_1$•NaI, projection of the structure along the *c* axis, and view of the unit cell slightly oblique to the *b* axis, with *c* vertical (4 pages). Ordering information is given on any current masthead page.

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Regioselective Functionalization of Pyridinesulfonic Acids. Ortho-Lithiation of Tertiary 2- and 4-Pyridinesulfonamides

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Tertiary 2- and 4-pyridinesulfonamides were ortho-lithiated at low temperature by an excess of lithium diisopropylamide. Proton abstraction occurs selectively at the more acid 3-positions in the two cases. 3-Lithio-2- and -4-(piperidinosulfonyl)pyridines reacted with such electrophiles as iodine, aldehydes, 3-pentanone, dimethylformamide, and carbon dioxide to give the corresponding ortho-disubstituted pyridines in high yields. Lithiation ability of the pyridinesulfonamides was also compared with that of the benzene analogue.

Electron-rich heteroaromatics such as pyrrole, furan, and thiophene easily undergo electrophilic substitution. However, this powerful synthetic tool can seldom be used with electron-deficient heteroaromatic compounds such as pyridine and quinoline. Metalation is another powerful and regioselective method for substituting aromatic derivatives,[1] but it has only recently been applied to pyridines[2] because of the peculiar reactivity of the pyridine ring toward nucleophilic metalating agents such as chelated alkyllithiums. A proper choice of reaction conditions allows the directed lithiation of pyridines that bear ortho-directing groups.[2]

Little work has been done on the metalation of compounds bearing a sulfur-containing substituent except for our recent short report on the metalation of tertiary 3-pyridinesulfonamides.[3] In the homoaromatic series,[4] a (*N*,*N*-dialkylamino)sulfonyl moiety is an effective ortho-directing group for metalation of sulfonic acids. These lithiations are carried out with nucleophilic chelated al-

kyllithiums, which are ineffective with pyridine analogues.[3,5] We report here on the metalation of 2- and 4-pyridinesulfonamides.

Results

2-[(*N*,*N*-Dialkylamino)sulfonyl]pyridines **1a–c** were prepared from commerical 2-pyridinethiol via 2-pyridinesulfonyl chloride.[6] 4-[(*N*,*N*-Dialkylamino)-sulfonyl]pyridines **2a–c** were obtained by a four-step sequence starting from commerical 4-nitropyridine *N*-oxide.[7]

Metalation of Pyridinesulfonamides. Lithiation of 2-pyridinesulfonamides **1a–c** was performed at low temperature by using an excess of lithium diisopropylamide (LDA). The 3-lithio derivatives **3a–c** were quenched with benzophenone at −70 °C to give **4a–c** in yields of 87–95%. Under similar conditions, 4-pyridinesulfonamides **2a–c** were substituted in the 3-position to give **6a–c**.

(1) For a general review of metalation, see: Wakefield, B. J. *The Chemistry of Organolithium Compounds*; Pergamon: Oxford, 1974. For a recent review of the scope of directed metalation, see: Gschwend, H. W.; Rodriguez, H. R. *Org. React. (N.Y.)* **1979**, *26*, 1.
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(4) Watanabe, H.; Schwartz, R. A.; Hauser, C. R.; Slocum, D. W. *Can. J. Chem.* **1965**, *47*, 1543.

(5) Abramovitch, R. A.; Ahmed, K. S.; Giam, C. S. *Can. J. Chem.* **1963**, *41*, 1752.
(6) 2-Pyridinesulfonyl chloride has been prepared by chlorination of 2-pyridinethiol.[7] Overall yields of **2a–c** are, respectively, 70%, 75%, and 80%.
(7) Ochiai, E. *J. Org. Chem.* **1953**, *18*, 538. Angulo, J.; Municio, A. M. *An. R. Soc. Esp. Fis. Quim., Ser. B.* **1960**, *56*, 395. The overall sequence is as follows: 4-chloropyridine *N*-oxide, 4-pyridinethiol *N*-oxide, 4-pyridinesulfonyl chloride *N*-oxide, and 4-[(*N*,*N*-dialkylamino)sulfonyl]-pyridine *N*-oxides. Overall yields of **1a–c** have been optimized to 50%, 35%, and 60%, respectively.