Peptide Side-Arm Derivatives of Lariat Ethers and Bibracchial Lariat Ethers: Syntheses, Cation Binding Properties, and Solid State Structural Data

Banita D. White, Jesus Mallen, Kristin A. Arnold, Frank R. Fronczek,† Richard D. Gandour,† Laura M. B. Gehrig,† and George W. Gokel*

Departments of Chemistry, University of Miami, Coral Gables, Florida 33124, and Louisiana State University, Baton Rouge, Louisiana 70809-1804

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Aza-18-crown-6 and 4,13-diaza-18-crown-6 derivatives having one or two side arms have been prepared. The side arms are of the form >N-Gly-AA-OMe, where "AA" is an amino acid. The 18-membered ring compounds were prepared by alkylation of aza-18-crown-6 as follows: Gly-Gly-OMe (**14**, 57%, mp 42–43 °C); Gly-Ile-OMe (**15**, 50%); Gly-Val-OMe (**16**, 56%). Two-armed compounds were obtained by alkylation of 4,13-diaza-18-crown-6 as follows: Gly-Gly-OMe (**18**, 58%, mp 118–119 °C); Gly-Ala-OMe (**19**, 50%, mp 62–63 °C); Gly-Phe-OMe (**20**, 65%, oil); Gly-Leu-OMe (**21**, 51%, mp 72–73 °C); Gly-Ile-OMe (**22**, 60%, oil); Gly-Val-OMe (**23**, 59%, oil). Sodium iodide complexes of **18**, **19**, and **20** were isolated. Solid state structural data are reported for **18** and its sodium complex, as well as its potassium complex that was reported in preliminary form (ref 9f). Compound **18** crystallizes in the triclinic space group $P\bar{1}$ with cell constants a = 9.0210 (8), b = 10.4768 (15), and c = 15.357 (2) Å, α = 87.457 (12)°, β = 87.119 (10)°, γ = 68.042 (9)°, and Z = 2 for D_c = 1.286 g cm^{-3}. Least-squares refinement based on 4034 observed reflections led to a final conventional R value of 0.041. The sodium iodide complex of **18** crystallizes in the monoclinic space group $P2_1/c$ with cell constants a = 9.732 (3), b = 17.710 (2), and c = 38.848 (3) Å, β = 96.99 (2)°, and Z = 8 for D_c = 1.430 g cm^{-3}. Least-squares refinement based on 5512 observed reflection led to a final conventional R value of 0.041. The potassium iodide complex of **18** crystallizes in the monoclinic space group $C2/c$ with cell constants a = 15.656 (4), b = 14.752 (3), and c = 26.784 (3) Å, β = 90.01 (2), and Z = 8 for D_c = 1.474 g cm^{-3}. Least-squares refinement based on 2595 observed reflections led to a final conventional R value of 0.035. There are two crystallographically independent molecules in each of the three crystal structures. The sodium and potassium complexes are compared to other BiBLE complexes and to cryptates. Cation binding affinities for these compounds have been assessed in anhydrous methanol and are reported here for Na^+ and K^+ cations.

Introduction

The naturally occurring ionophore valinomycin[1] possesses a number of interesting properties. Although it is a 36-membered ring, it is highly selective for K^+ among the alkali and alkaline-earth metals.[2] This contradicts the hole-size concept[3] that applies to many, more rigid, structures. The compound is composed of a highly lipophilic surface that no doubt facilitates its ionophoric ability. The structure alternates amino and hydroxy acids. Thus, ester carbonyl donor groups alternate with amide carbonyl groups. Although it seems reasonable at first to suppose that the amide carbonyl groups would function as donors for hard alkali metal ions, only the ester carbonyl groups do so.[4] A final observation is that each of the 12 subunits in this cyclododecadepsipeptide is chiral and the chirality alternates $(D,D,L,L)_3$. It was our intent at the outset of the lariat ether program to understand these observations and to utilize such knowledge to synthesize simpler structures having the same essential features as valinomycin.

Certain of the observations noted above can readily be understood. The amide carbonyl groups, for example, are involved in conformation-holding hydrogen bonds,[4] leaving only ester carbonyl groups to bind the cation. The large ring folds into a "tennis-ball seam"[5] arrangement, making it like the three-dimensionally enveloping cryptands.[6] At the time this work was begun, the reason for alternating chirality was less obvious to us and we hoped to unravel some of this apparent mystery by comparing binding constants and structures in a variety of N-pivot lariat ethers[7] having peptide or dipeptide side arms. The chirality now appears to be a device that permits the molecule to fold into the appropriate binding conformation while maintaining the dynamics required for transport. Even though this aspect of valinomycin's structure can now be explained, and the compounds prepared fail to mimic valinomycin's binding profile, these compounds do exhibit a number of interesting features described hereinafter.

Results and Discussion

We have previously reported the syntheses and considerable binding and structural information for the single-armed, nitrogen-pivot lariat ethers[8] and their two-armed

† Louisiana State University.

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relatives, the bibracchial lariat ethers or BiBLEs.[9] Although we generally considered that the BiBLEs would be better models for valinomycin and would thus reveal more about the latter's binding properties, we prepared a series of single-armed analogues for comparative purposes. We have now obtained detailed binding information on both groups of compounds, thermodynamic parameters for compounds **18**, **19**, **24–26**, and the crystal structures of two complexes.

Side-Arm Syntheses. Our strategy was to prepare several dipeptide side-arm precursors and then attach them to the macroring nitrogen atom(s). The simplest series of dipeptides one can envision has glycine attached to a second amino acid. In such a series, the chirality of only one amino acid must be considered and synthetic access should, in principle, be facilitated. Model studies on aza-15-crown-5 derivatives were conducted initially since the glycine derivative of aza-15-crown-5, *N*-(carboxymethyl)aza-15-crown-5, was readily available. Several attempts to prepare aza-15-crown-5-Gly-amino acid derivatives from aza-15-crown-5-Gly-OH and L-valine methyl ester hydrochloride (**7**) using coupling methods (DCC,[10] mixed anhydride[11]) proved unfavorable. Purification of the isolated product was often difficult (DCC method[10]) and yields were poor (15% yield) when the mixed anhydride method[11] was used.

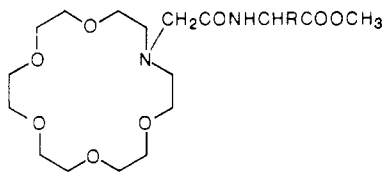
Our final strategy involved a two-step approach. In the first step, the amino acid methyl ester hydrochloride salts were converted to their *N*-chloroacetyl derivatives. The N-substituted aza-18-crown-6 derivative was then obtained by N-alkylation of the parent crown.

$ClCH_2COCl + H_2NCHRCOOCH_3 \rightarrow$

3–7

$ClCH_2CONHCHRCOOCH_3$ (aza-18-crown-6) →

8–13



14–17

3, **9**: R = CH_3
4, **10**: R = CH_2Ph
5, **11**: R = $CH_2CH(CH_3)_2$
6, **12**, **15**: R = $CH_3CHCH_2CH_3$
7, **13**, **16**: R = $CH(CH_3)_2$
17: side arm = $CH_2COOCH_2CH_3$

Syntheses of Amino Acid Methyl Ester Hydrochloride Salts. The amino acid methyl ester hydrochloride salts were synthesized by conventional methods [see Experimental Section, CH_3OH, HCl(g)] in high yields. The following amino acid methyl esters were prepared: L-alanine (**3**, 97%, mp 88 °C), L-phenylalanine (**4**, 98%, mp 157–158 °C), L-leucine (**5**, 95%, mp 130–132 °C), L-isoleucine (**6**, 94%, mp 82–85 °C), and L-valine (**7**, 98%, mp 170–172 °C). Three of the esters (**4**, **5**, and **7**) were purified by recrystallization from acetone. Compounds **3** and **6** proved hygroscopic and were isolated after trituration of the thick oils under diethyl ether. The melting points and optical rotations correspond to published values.[12]

Table I. *N*-Chloroacetyl Amino Acid Methyl Ester Derivatives

no.	R	yield (%)	bp (°C/0.05 torr) (mp, °C)	$[\alpha]^{25}_D$,[a] deg
8	H	51	70–75 (41–43)	*b*
9	Me	50	65–70 (34–35)	−50.5
10	benzyl	97	115–120 (68–71)	+10.3
11	*i*-Bu	84	80–85	−27.7
12	*s*-Bu	92	65–70	−7.9
13	*i*-Pr	83	60–65 (44–46)	−15.2[c]

[a] Rotations were measured in MeOH (*c* = 2). [b] Achiral. [c] Also measured in H_2O, $[\alpha]^{25}_D$ = −33.1° (*c* = 2.75, H_2O).[13]

Table II. Dipeptide Derivatives of Aza-18-crown-6 and 4,13-Diaza-18-crown-6

no.	side arm	yield (%)	bp [°C/0.05 torr], or (mp, °C)	$[\alpha]^{22}_D$, deg (*c* = 2, MeOH)
	Aza-18-crown-6 Derivatives			
14	$CH_2CONHCH_2COOMe$	57	(42–43)	[a]
15	$CH_2CONHCH(s\text{-}Bu)COOMe$	50	180–185	−0.2
16	$CH_2CONHCH(i\text{-}Pr)COOMe$	56	175–180	−5.5
	4,13-Diaza-18-crown-6 Derivatives			
18	Gly-Gly-OMe	58	118–119	[a]
19	Gly-Ala-OMe	50	62–63	−19.3
20	Gly-Phe-OMe	65	oil	−1.75
20·NaI		82	183–184	−7.1
21	Gly-Leu-OMe	51	72–73	−15.8
21·NaI		72	104–105	−36.2
22	Gly-Ile-OMe	60	oil	−3.1
22·NaI		61	120–121	−19.4
23	Gly-Val-OMe	59	oil	−3.25

[a] Achiral.

Syntheses of *N*-Chloroacetyl Amino Acid Ester Derivatives. The *N*-chloroacetyl derivatives of **3–7** (i.e., **8–13**) were readily prepared from chloroacetyl chloride and Na_2CO_3 in CH_2Cl_2. The weak base was chosen to minimize racemization. The derivatives prepared, their yields, and their calculated specific rotations are shown in Table I.

The amino acid ester was first dissolved in H_2O (pH 2) and the solution adjusted (Na_2CO_3) to pH 10. The free amine was extracted with CH_2Cl_2, dried (Na_2SO_4), and then treated with chloroacetyl chloride. The yields reported in Table II assume that an equimolar amount of the free amino acid was extracted. The lower yields of **8** and **9** may be attributed to the higher water solubility of the free amine (in saturated Na_2CO_3 solution). Compounds **8**,[14] **9**,[15] and **13**[13] have been previously prepared. Their melting points or boiling points and optical rotations were identical with those reported.

Syntheses of Aza-18-crown-6 Amino Acid Derivatives. The *N*-(amino acid)aza-18-crown-6 derivatives were

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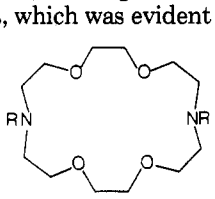
prepared by heating the appropriate chloroacetyl precursor (2 equiv) with aza-18-crown-6 (1 equiv), NaI (2 equiv), and Na_2CO_3 (2 equiv) in refluxing acetonitrile. Yields ranged from 50% to 57% and are recorded in Table II for chemically pure, isolated materials. Since these compounds had not been reported previously, we attempted to assess the extent of racemization, if any, by the following experiments. Compound **16** and the side-arm precursor to **16**, i.e., **13**, were maintained under the reaction conditions. Sodium iodide was eliminated from the mixture containing **13** since the undesirable iodide derivative could form. The rotation for the crown compound, **16**, decreased approximately 7% during the time required for the reaction. The rotation for the side-arm precursor, **13**, decreased approximately 0.5%. In a separate experiment, an L-*N*-(chloroacetyl)amino acid ester was mixed with an equimolar amount of *N*-methylmorpholine in refluxing MeCN. Aliquots were removed at regular intervals during 12 h. When the side arms were Cl-Gly-Ala-OMe, Cl-Gly-Val-OMe, and Cl-Gly-Phe-OMe, the optical rotations diminished 8%, 11.5%, and 13.4%, respectively, during this period. Thus, some racemization probably occurs under the reaction conditions, but it is not extensive.

Purification of the aza-crown involved column chromatography of the NaI complexes over a column of silica gel (3% $MeOH/CH_2Cl_2$ as eluent). The complexes were isolated but could not be crystallized. The thick oils obtained after chromatography were then dissolved in CH_2Cl_2 and washed with H_2O. Partial hydrolysis of the crown was evident by TLC analysis (silica, 10% $MeOH/CH_2Cl_2$) from the formation of a material having a lower R_f value after washing. The oils (**15** and **16**) were then chromatographed through a short column of silica followed by Kugelrohr distillation. Compound **14** was obtained after recrystallization from ether.

Syntheses of N,N′-Disubstituted Amino Acid Derivatives. The amino acid derivatives were prepared by dialkylation of 4,13-diaza-18-crown-6 by using the appropriate *N*-chloroacetyl amino acid derivative. Purification of the diaza-crowns involved preparative chromatography of the NaI complex over a column of silica gel. In some cases, the complex was isolated directly from the reaction mixture (e.g. **18**·NaI) or by trituration of the oil obtained after chromatography (Et_2O, **19**·NaI and **20**·NaI). Recrystallization of the complex and subsequent washing (H_2O) gave the uncomplexed diaza-crown. Like the aza-18-crown-6 derivatives, washing of the complex gave partial side-arm hydrolysis, which was evident from TLC analysis.



18, R = Gly-Gly-OMe
19, R = Gly-Ala-OMe
20, R = Gly-Phe-OMe
21, R = Gly-Leu-OMe
22, R = Gly-Ile-OMe
23, R = Gly-Val-OMe

Racemization studies similar to those described for the single-armed materials were conducted on the diaza system. 4,13-Diaza-18-crown-6 derivatives having Gly-Ala-OMe (**19**), Gly-Phe-OMe (**20**), or Gly-Val-OMe (**23**) were refluxed in MeCN for 12 h in the presence of 2 equiv each of Na_2CO_3 and NaI. Optical rotations (25 °C in MeCN) decreased 2.3%, 3.7%, and 6% respectively.

Cation Binding Properties. Binding properties for 18-membered aza and diaza macrocycles having amino acid containing side arms (anhydrous MeOH, 25 °C) are reported in Table III as decadic logarithms. Compounds having *n*-propyl, Gly-OEt, and Gly-NH_2 side arms are included for comparison.

Table III. Syntheses and Cation Binding Properties at 25 °C of Peptide-Derived Lariat Ethers and BiBLEs

no.	side arm[a]	yield, %	log K_s in MeOH Na^+	log K_s in MeOH K^+
	Aza-18-crown-6 Derivatives			
14	$CH_2CONHCH_2COOCH_3$	57	3.50	4.53
15	$CH_2CONHCH(s\text{-}Bu)COOCH_3$	50	4.03	5.10
16	$CH_2CONHCH(i\text{-}Pr)COOCH_3$	56	4.04	5.03
17	$CH_2COOCH_2CH_3$	79	4.67	5.92
	$CH_2CH_2CH_3$		3.50	4.92
	4,13-Diaza-18-crown-6 Derivatives			
18	$CH_2CONHCH_2COOCH_3$	58	3.35	3.32
19	$CH_2CONHCH(Me)COOCH_3$	50	4.36	4.21
21	$CH_2CONHCH(i\text{-}Bu)COOCH_3$	51	4.26	4.17
22	$CH_2CONHCH(s\text{-}Bu)COOCH_3$	60	4.16	4.09
23	$CH_2CONHCH(i\text{-}Pr)COOCH_3$	59	4.18	4.11
24	$CH_2CH_2CH_3$	78[b]	2.86	3.78
25	CH_2COOCH_3	92[c]	5.51	5.78
26	CH_2CONH_2	61[d]	3.77	3.75

[a] Attached at the macroring nitrogen atom(s); all chiral centers have the L configuration. [b] Reference 9c,d. [c] Reference 9a. [d] Kulstad, S.; Mulmsten, L. A. *Acta Chem. Scand. Ser. B.* **1979**, *B33*, 469.

Cation Binding Properties. The aza-18-crown-6 amino acid derivatives' Na^+ binding constants range from (log K_s) 3.50 to 4.04 and the K^+ binding constants range from (log K_s) 4.53 to 5.10. The K^+ binding constants are approximately an order of magnitude greater than the Na^+ binding constants. The binding constants are lower than expected on the basis of the results for the aza-crown having an *n*-propyl side arm and the aza-crown with a side arm containing an ester donor, **17**. Compound **14**, which has a glycyl–glycine side arm, has the same binding constant for Na^+ and a lower binding constant for K^+ than the *n*-propyl side-armed aza lariat. [(Ethoxycarbonyl)-methyl]aza-18-crown-6, compound **17**, has the following cation binding constants: log K_s for Na^+, 4.67; log K_s for K^+, 5.92. The amide functional group is more polar than the ester functional group and the amide-side-armed lariat ethers were expected to exhibit higher binding constants than the ester derivatives. This was not the case although the Na^+ and K^+ binding constants for the aza-18-crown-6 lariat ethers having side arms containing amino acids are generally higher than those observed for similar structures containing only ether donors.

The diaza-18-crown-6 amino acid derivatives, compounds **18**–**23**, also displayed lower binding ability than the ester BiBLE, compound **25**. The binding constants for the dipeptide BiBLE derivatives ranged from (log K_s) 3.35 to 4.36 for Na^+ and (log K_s) 3.32 to 4.21 for K^+. These values are even lower than the Na^+ and K^+ cation binding constants observed for *N,N′*-bis(2-methoxyethyl)-4,13-diaza-18-crown-6, which contains fewer polar ether donor groups (log K_s for Na^+ is 4.75, and log K_s for K^+ is 5.46).[9a]

The selectivity for K^+ observed in the single-armed systems is lost in the two-armed systems. With the exception of compounds **14** and **18**, the glycylglycine derivatives, the Na^+ binding is slightly stronger in the diaza-crowns than in the aza-crowns. The K^+ binding constants for all of the aza-18-crown-6 peptide derivatives are markedly higher than for the two-armed analogues. The diminished K^+ binding strength in the latter case accounts for the reduced K^+/Na^+ selectivity. The K^+ cation fits an 18-membered macroring and is generally observed (X-

Table IV. Sodium Cation Binding Constants at 25 °C and Thermodynamic Parameters for 4,13-Diaza-18-crown-6 Derivatives Having Peptide Side Arms

no.	side arm	log K_s	ΔH, kcal/mol	$T\Delta S$, kcal/mol
18	$CH_2CONHCH_2COOCH_3$	3.45	−1.39 ± 0.14	3.33 ± 0.13
19	$CH_2CONHCH(Me)$-$COOCH_3$	4.40	−7.54 ± 0.12	−1.53 ± 0.09
24	*n*-propyl	2.86	−2.82 ± 0.05	1.08 ± 0.04
25	CH_2COOCH_3	5.49	−6.18 ± 0.07	1.30 ± 0.05
26	CH_2CONH_2	3.77	−4.60 ± 0.18	0.53 ± 0.19

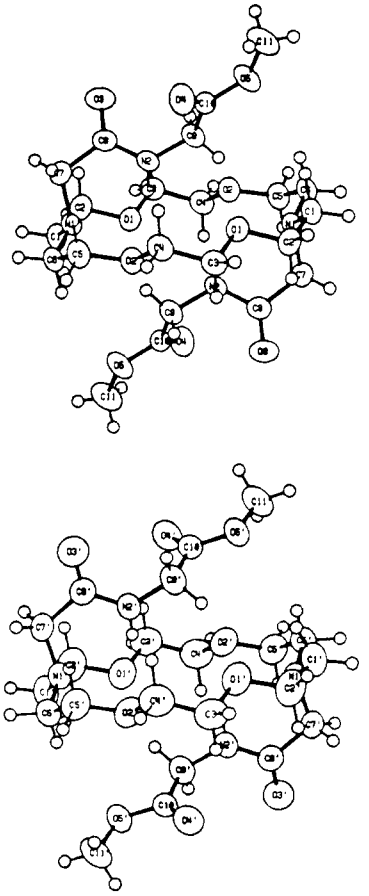


Figure 1. Drawings of both molecules of *N,N'*-bis(Gly-Gly-OMe)-1,10-diaza-18-crown-6.

ray analysis) to be in the plane of the macroring when bound. The K^+ binding constant is therefore affected more than the Na^+ binding constant by the loss of the macroring oxygen donor and replacement by a less effective nitrogen donor.

We attempted to obtain Ca^{2+} binding constants for the amino acid lariat ether derivatives using our standard method of competing Na^+ and Ca^{2+} cations and detecting the Na^+ cations using a sodium selective glass electrode.[3] No competition between Na^+ and K^+ was observed, indicating strong complexation to the Ca^{2+}.

Thermodynamic Parameters. The enthalpic and entropic components of the binding constants were obtained for BiBLE derivatives **18**, **19**, and **24–26**. The data are reported in Table IV. The thermodynamic parameters for glycyl-glycine derivative **18** are of special interest since this compound bound cations less effectively than the other amino acid derivatives in both the aza and diaza series. This suggests that the complexation process for the glycyl-glycine compound is different than for the other amino acid derivatives.

In the liquid phase, it is unclear whether the dipeptide

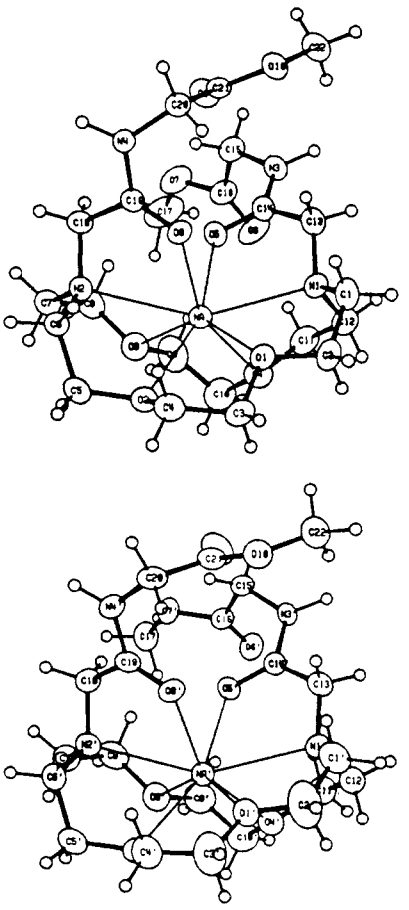


Figure 2. Drawings of both sodium iodide complexes of *N,N'*-bis(Gly-Gly-OMe)-1,10-diaza-18-crown-6.

amide carbonyl participates in binding or both the amide and ester carbonyl groups are involved. Examination of CPK, space-filling, molecular models indicates that the amide carbonyl is within bonding distance of the cation, but the ester carbonyl may be too remote to interact. The X-ray crystal structures obtained when **18** was complexed with NaI or KI (see Figures 1 and 2) both show that of the side-arm donors, only the amide carbonyl groups participate in binding. It is, of course, inappropriate to assume that this is also the case for the other amino acid derivatives. Differences in binding behavior noted above also suggest that the complexation processes differ for the other derivatives.

Like the binding constants, the thermodynamic parameters obtained for compound **18**, which has glycyl-glycine side arms, also suggest different binding behavior for this compound. Compound **18** forms an entropy-dominated complex while the other complexes are enthalpy-dominated. Since the portion of the side arm not involved in binding should be more flexible than if the side arm is complexed, some disordering of the bulk solvent leads to a favorable entropy effect.

Complexation of **24**, which has *n*-propyl side arms, is less enthalpically favored than complexation by **19**, **25**, and **26**, which have side-arm donor groups placed appropriately to participate in binding the cation. The most favorable complexation enthalpy is observed for compound **19**, which has glycyl-alanine side arms, even though the overall binding constant is lower than for compound **25**, which has an ester donor in the side arm. This may indicate that the ester carbonyl on the side arm of **19** interacts weakly along with the amide carbonyl in binding the cation. Such an interaction could be due to increased lipophilicity of a

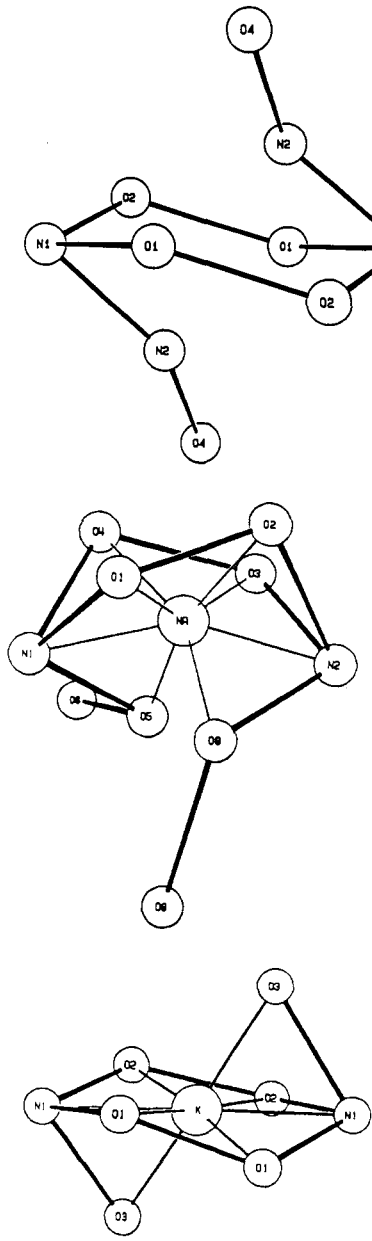


Figure 3. Skeletal drawings of both molecules of 18 (top) uncomplexed, (middle) sodium complex, (bottom) potassium complex.

methyl-group-induced conformational effect.

Structural Properties. In order to better understand how the side arm participates in binding and to determine the structures of metal cation complexes, X-ray crystallographic studies were undertaken. The atomic positional parameters for 18 and its sodium and potassium complexes are presented in Tables A–C in the supplementary material. In addition, selected torsion angles and tables of hydrogen atom coordinates, anisotropic thermal parameters, distances, and angles may be found in the supplementary material.

There are two independent molecules in each of the three crystals. The structures of the uncomplexed BiBLE and its sodium complex are shown in Figure 1. The potassium complexes have been described previously.[9f] All six molecules are compared in Figure 3 as skeletal drawings that emphasize the arrangement of donor atoms about the cations. The skeletal and structural drawings of *N,N'*-bis[*N''*-acetylglycyl]-4,13-diaza-18-crown-6 methyl ester, 18, are shown in Figures 1a and b. Structures of the Na^+ complexes of 18 are shown in Figure 2. Structural features are compared in Figures 1–3 and are discussed below.

Uncomplexed Diaza-crown. The X-ray structure of *N,N'*-bis[*N''*-acetylglycyl]-4,13-diaza-18-crown-6 methyl ester, 18, is shown in Figures 1a and 1b. Three points are notable. The side arms are in an anti relationship about the macrocycle's plane and reach completely over the macroring above and below the plane. The oxygen atoms of the four carbonyl groups are pointed away from the cavity, which is expected in the absence of a cation. The amide hydrogens are directed into the cavity and they hydrogen bond to their respective nitrogen pivot atoms. Both molecules are centrosymmetric and differ slightly in their conformations. (The largest difference in torsion angle is 16°). The donor atom framework adopts a pseudo-D_{3d} conformation.

The two independent molecules of Na^+·18 complex are shown in Figure 2. The macroring in both complexes adopts a C_i conformation with both of the pendant groups on the same side of the macroring. Both structures are chiral and differ only slightly. (The largest difference in torsion angle is 19°.) The skeletal drawings (Figure 3) reveal that the macroring donor atoms adopt a twist-boat conformation, with the amide oxygen atom on each side arm completing the encapsulation of the cation.

The KI complex of 18 (mp 118–119 °C) crystallizes with equal numbers of two independent complex cations; one contains a crystallographic 2-fold symmetry axis ($K{\cdot}18_2$) and one is centrosymmetric ($K{\cdot}18_c$). Skeletal drawings of both complexes are shown in Figure 3. The 2-fold symmetric complex has unprimed labels while those of the centrosymmetric complex are primed. In both complexes, the macroring is in a D_{3d} conformation with one side arm above and one below the macroring. In the 2-fold, symmetric complex, the potassium ion lies approximately on the line connecting the two macroring nitrogens as well as on a line connecting O1 and O2, but the O3–K–O3 angle is 157.4 (1)°. In the centrosymmetric complex, the potassium lies on the inversion center, on all lines connecting donors with their symmetric counterparts.

The most significant differences between the two complexes are observed in the side arms. As viewed in Figure 1, both side arms in the 2-fold symmetric complex coil to the back. In the centrosymmetric complex, the side arm on the bottom coils to the back while the side arm on top coils to the front. The biggest difference is the potassium donor distance: K–O3, 2.841 (3) Å vs K'–O3', 2.638 (3) Å. Consequently, the centrosymmetric complex has a smaller cavity (R = 1.375 Å) than the 2-fold symmetric complex (R = 1.411 Å). The angles for complexation by the amide carbonyl are similar: K–O3–C8, 121.0 (2)° vs K'–O3'–C8', 125.8 (2)°. The potassium ion does not lie in the plane of the carbonyl in either complex. For the 2-fold symmetric complex, the torsion angle K–O3–C8–C7 is –18.0° and the metal ion lies on the *si* face of both carbonyl groups. On the other hand, in the centrosymmetric complex, the metal ion is farther out of plane, K'–O3'–C8'–C7' is 32.0°, and is located on the *si* face of one carbonyl and on the *re* face of the other. Except for the sign changes in the torsion angles of the peptide side arms, only C3–N1–C7–C8 differs greatly: –137.3° in the centrosymmetric complex; –157.5° in the 2-fold symmetric complex.

The crystallization of the two independent complexes of different symmetry points out the difference in chirality in the complexed form. The 2-fold symmetric complex is chiral and both enantiomers are present, while the centrosymmetric complex is achiral. This phenomenon may be compared to the situation in which there is no stereo-

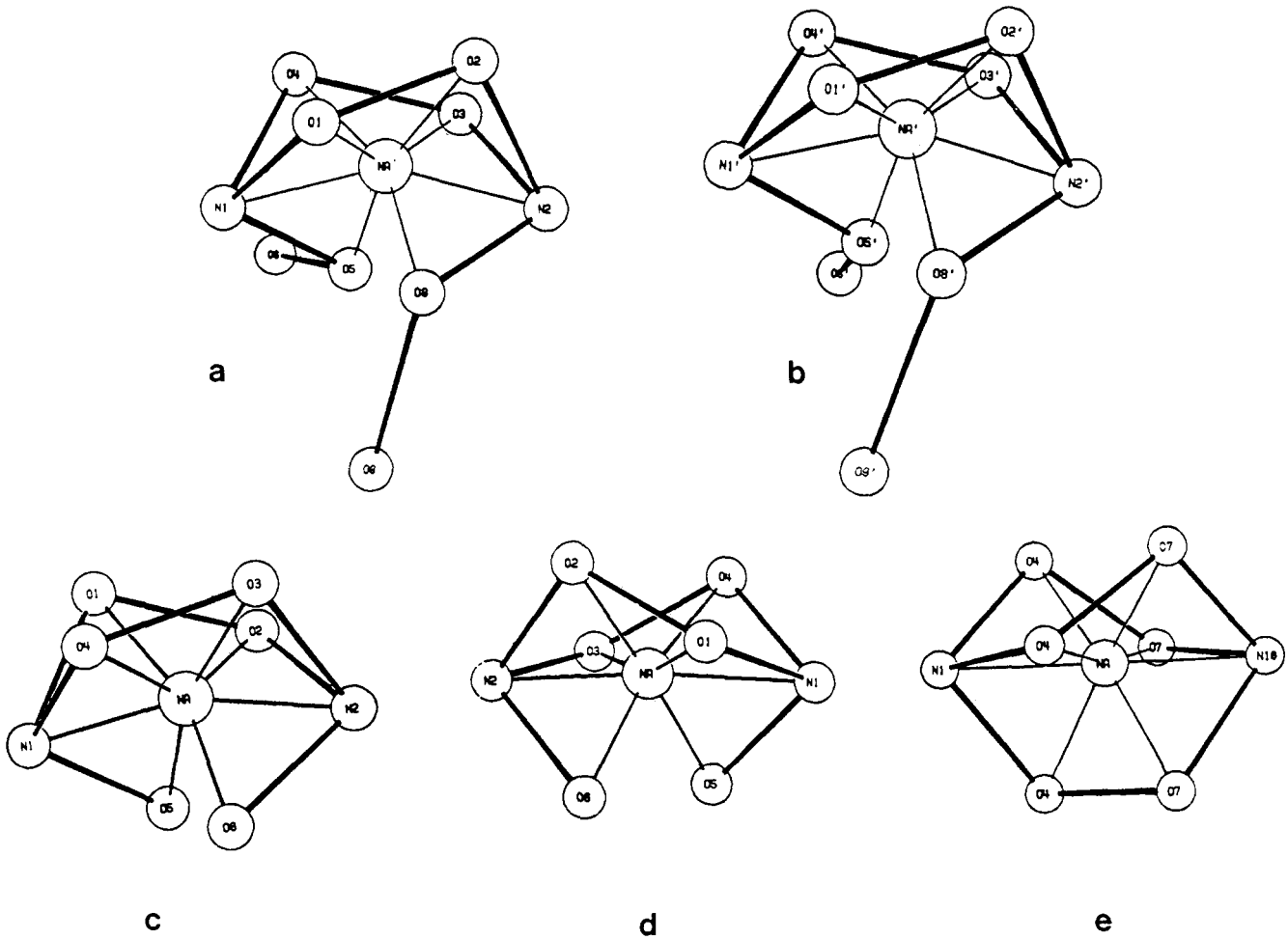


Figure 4. Skeletal drawings of (a) Na·A1-22-1A, (b) Na·A'1-22-1A', (c) Na·1-22-1, (d) Na·H1-22-1H, (e) Na·222.

Table V. Comparison of Selected Structural and Binding Parameters of Sodium Complexes of BiBLEs and 22 Cryptand

				A1-22-1A	
interaction	222[a]	1-22-1[b]	H1-22-1H[c]	2-fold	centrosymmetric
Na-O, Å	2.582	2.572	2.611	2.471	2.515
	2.582	2.582	2.437	2.526	2.567
	2.582	2.486	2.590	2.556	2.598
	2.566	2.669	2.564	2.530	2.571
	2.566				
	2.566				
side arm		2.488	2.426	2.413	2.380
		2.614	2.588	2.432	2.496
Na-N, Å	2.782	2.838	2.630	2.640	2.692
	2.722	2.677	2.637	2.664	2.651
R, Å	1.19	1.19	1.14	1.10	1.13
N-Na-N, deg	180	174.8	159.5	151.1	151.2
N-N, Å	5.504	5.509	5.183	5.135	5.158
coordn no.	8	8	8	8	8
log K_s	7.98[d]	4.75[e]	4.87*e*	3.35	

[a] Reference 17. [b] Reference 9g. [c] Reference 8b. [d] Reference 18. [e] Reference 9a.

Table VI. Comparison of Selected Structural and Binding Parameters of Potassium Complexes of BiBLEs and 222 Cryptand

				A1-22-1A	
interaction	222[a]	1-22-1[b]	H1-22-1H[b]	2-fold	centrosymmetric
K-O, Å	2.776	2.848	2.834	2.786	2.772
ring	2.776	2.848	2.834	2.786	2.772
	2.789	2.803	2.848	2.733	2.792
	2.789	2.803	2.848	2.733	2.792
	2.790				
	2.790				
side arm		2.860	2.721	2.841	2.638
		2.860	2.721	2.841	2.638
K-N, Å	2.874	2.941	3.128	2.985	2.999
	2.874	2.941	3.128	2.985	2.999
R, Å	1.38	1.438	1.46	1.411	1.376
N-K-N, deg	180	180	176.4	176.2	1.80
N-N, Å	5.748	5.882	6.253	5.958	5.998
coordn no.	8	8	8	8	8
log K_s	10.41[c]	5.46[d]	5.08[d]	3.32	

[a] Reference 19. [b] Reference 8b. [c] Reference 18. [d] Reference 9a.

selectivity in the formation of diastereomers of which one diastereomer is a meso compound.

The complexes exhibit a topography similar to that observed for the related 18-membered macrocyclic BiBLE having 2-oxabutyl side arms and to that observed by others for the complexation of copper ion with carboxylatomethyl side arms.[16] This anti binding, one arm on top and the other on the bottom, is probably the preferred topography for cations with radii equal to or larger than that of K^+.

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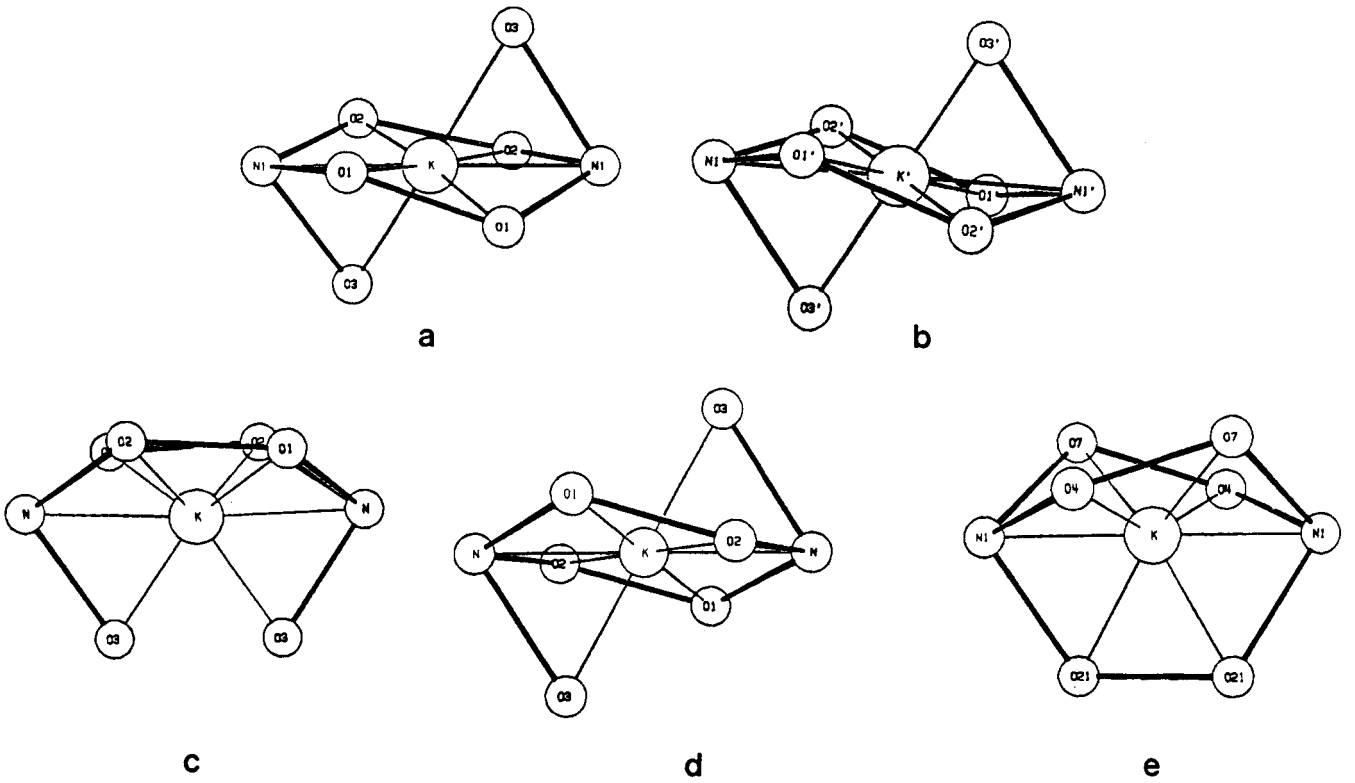

Figure 5. Skeletal drawings of (a) K^+·A1-22-1A, (b) K^+·A'1-22-1A', (c) K^+·1-22-1, (d) K^+·H1-22-1H, (e) K^+·222.

The only exception thus far observed is the cryptate-like topography of the potassium complex of the 18-membered ring diaza-BiBLE having 2-hydroxyethyl side arms.[8]

Structural Comparison of BiBLE and Cryptate Complexes. The donor group arrangements in the sodium cation complexes of 18 (A1-22-1A), bis(2-hydroxymethyl)-4,13-diaza-18-crown-6 (H1-22-1H), bis(3-oxabutyl)-4,13-diaza-18-crown-6 (1-22-1), and 2.2.2-cryptand[17-19] (222) are shown in Figure 4 and potassium cation complexes are illustrated in Figure 5. Binding and structural data for Na^+ complexes are presented in Table V and for K^+ in Table VI.

The sodium cation complexes of 18 have the macroring donors in the twist-boat conformation. This conformation, seen in the macroring framework of simple coronates as well, better encapsulates the sodium cation, which is smaller than the potassium cation. In the complexes of A1-22-1A and H1-22-1H the nitrogen atoms of the macroring are located at the bow and stern of the (donor framework) boat, while in 1-22-1 and 222 the nitrogen atoms are located along the gunwales. As a consequence of this positioning, the N–N distance is shorter and the N–Na–N angle is smaller in the former than in the latter complexes. The Na–O distances for the side arms as well as the mean cavity radii, R_s, increase in the order amido < hydroxyl < methoxyl. This order is inverse to the oxygen donor group's electron density and suggests that the stronger (more electronegative) the donor, the shorter the Na–O distance. Octacoordinated sodium cation has an effective ionic radius of 1.18 Å. Complexes with all ether oxygens, 1-22-1 and 222, have R_s close to this value, but H1-22-1H and A1-22-1A have significantly smaller R_s due to the closer contact of the side-arm donors.

Two of the BiBLE complexes of potassium cation have the macroring in a chair conformation with the side arms anti and the cation located in or near the macroring's donor atom plane. The one exception is H1-22-1H, which adopts a cryptand-like conformation. We have pointed out that this complex is unique[9g] because the hydroxyls are small enough to fit on the same side of the complex. The two potassium complexes of A1-22-1A differ significantly in the K–O side-arm distances, 2.841 (3) Å vs 2.638 (3) Å, and R_s, 1.411 Å vs 1.376 Å. The amido complexes have smaller R_s values than do the methoxyl and hydroxyl complexes, which reflects the stronger donor character of amido that is seen in the sodium complexes. The unique topology of the 1H-22-1H potassium complex makes quantitative correlations difficult. Octacoordinated potassium has an effective ionic radius[20] of 1.51 Å. All of the K^+ complexes have R_s smaller than this with values ranging from 1.37 to 1.46 Å. These values compare favorably to effective ionic radii of K^+(VI), 1.38 Å, and K^+(VII), 1.46 Å. We have suggested[8b] that this is because nitrogen is a poor donor relative to oxygen toward alkali metals.

The poorer binding of sodium and of potassium cation to 18 than to other BiBLEs containing ethereal or hydroxylic oxygens as donors on the side arms is not apparent from the crystal structures. This may be due to the energy required to organize the side arm for complexation. The side arm is oriented with the amido nitrogen pointing into the cavity. To complex a cation, this conformation must be disrupted and the amido group rotated so that the oxygen bonds to the metal ion. Log K_s is a measure of the relative stability of the uncomplexed and complexed state. Because the uncomplexed state is relatively stable in 18 compared to the other BiBLES, it has a lower K_s. The huge differences in enthalpic and entropic contributions to binding by 18 and 19 suggest that side-arm conforma-

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tion and its effect on solvent reorganization play a crucial and not completely understood role in determining binding strength and selectivity.

Summary

An extensive and detailed study of 18-membered lariat ethers having one and two side arms of the form >N-Gly-AA-OCH_3, where AA is an amino acid, has been conducted. Unlike valinomycin, the amide rather than the ester carbonyl group is involved in binding. The fate of the second carbonyl group in each side arm appears determined by side-arm conformational effects. Although cation binding strengths and selectivities do not vary over a wide range, the enthalpic and entropic components exhibit a broad range of values. This variation is especially striking for **18** whose enthalpic contribution to binding is less than that found for **24**, a BiBLE lacking side-arm donor groups. In compound **18**, the poor enthalpy of binding must be due to a high price in conformational energy that must be paid by this relatively rigid side arm when it reorganizes. In general, the present work clearly demonstrates that only a combination of solution and solid state analyses can afford the appropriate perspective on cation binding interactions.

Experimental Section

^1H NMR spectra were recorded on a Varian EM 360A NMR spectrometer or on a Hitachi Perkin-Elmer R-600 high resolution NMR spectrometer in $CDCl_3$ solvents and are reported in ppm (δ) downfield from internal Me_4Si. ^{13}C NMR spectra were recorded on a Varian XL 100 NMR spectrometer or as noted above. Infrared spectra were recorded on a Perkin-Elmer 298 or a Perkin-Elmer 599 infrared spectrophotometer and were calibrated against the 1601 cm^{-1} band of polystyrene. Optical rotations were measured on a Perkin-Elmer Model 241 polarimeter in a glass microcell (100-mm path length, 1-mL volume) with a Na gas discharge lamp as the light source. Melting points were determined on a Thomas-Hoover apparatus in open capillaries and are uncorrected. Thin layer chromatographic (TLC) analyses were performed on aluminum oxide 60 F-254 neutral (Type E) with a 0.2-mm layer thickness or on silica gel 60 F-254 with a 0.2-mm layer thickness. Preparative chromatography columns were packed with activated aluminum oxide (MCB 80–325 mesh, chromatographic grade, AX 611) or with Kieselgel 60 (70–230 mesh). Chromatotron chromatography was performed on a Harrison Research Model 7924 chromatotron with 2-mm circular plates prepared from Kieselgel 60 PF-254. Gas chromatographic analyses were conducted on a Varian Associates Model 920 analytical gas chromatograph equipped with a thermal conductivity detector and a 5 ft × 0.25 in. column packed with 1.5% OV-101 on 100/120-mesh Chromosorb G. Helium was used as the carrier gas, and the flow rate was ca. 60 mL/min.

All reactions were conducted under dry N_2 unless otherwise noted. Each reagent was the best grade commercially available and used without further purification. Molecular distillation temperatures refer to the oven temperature of a Kugelrohr apparatus. Combustion analyses were performed by Atlantic Microlab, Inc., Atlanta, GA, and are reported as percents. Binding constants were measured in absolute MeOH at 25 ± 1.0 °C using a Corning 476210 electrode and an Orion Model 701A "ionalyzer" meter according to the method of Frensdorff[21] as previously described.[22] Samples suitable for single-crystal X-ray analysis were grown by slow cooling of a warm saturated solution, by evaporation of a saturated solution, or by vapor diffusion.

Aza-18-crown-6[7] and 4,13-diaza-18-crown-6[9] were prepared as described previously.

Preparation of Amino Acid Methyl Ester Hydrochloride Salts. The amino acid was mixed in MeOH and cooled to 0–5 °C with an ice–H_2O bath. A steady stream of HCl gas was bubbled into the mixture for ca. 1 h. During the first 15 min the insoluble amino acid became soluble in MeOH as the hydrochloride salt of the amino acid was formed. The temperature of the solution increased to 35 °C while still in the cooling bath. The solution was then allowed to stir at room temperature for 5 h. Evaporation of the solvent gave the amino acid methyl ester hydrochloride as a white solid, which was recrystallized from the solvent reported herein.

L-**Alanine methyl ester hydrochloride (3)** was prepared from L-alanine (10.0 g, 0.11 mol). Recrystallization of the crude product (THF) gave pure **3** (14.9 g, 97%) as a white hygroscopic solid, which had properties identical with those previously reported,[23] mp 100 °C, $[\alpha]^{28}_D$ = +6.8° (*c* = 2, MeOH) [lit.[23] mp 108 °C, $[\alpha]^{22}_D$ = +5° (*c* = 2, MeOH)].

L-**Phenylalanine methyl ester hydrochloride (4)** was prepared from L-phenylalanine (10.0 g, 0.06 mol). Recrystallization of the crude product (acetone) gave pure **4** (12.3 g, 95%) as a white solid with properties identical with those reported,[12] mp 158–159 °C, $[\alpha]^{29}_D$ = +36.2° (*c* = 2, EtOH) [lit.[12] mp 158–162 °C, $[\alpha]^{20}_D$ = +32.4° (*c* = 2, EtOH)].

L-**Leucine methyl ester hydrochloride (5)** was prepared from L-leucine (30.0 g, 0.23 mol). Recrystallization of the crude product (acetone) gave pure **5** (39.6 g, 95%) as a white solid, which had properties identical with those reported,[12] mp 130–132 °C, 145 °C dec, $[\alpha]^{24}_D$ = +12.6° (*c* = 2, H_2O) [lit.[12] mp 148–150 °C dec, $[\alpha]^{22}_D$ = +13.0° (*c* = 2, H_2O].

L-**Isoleucine methyl ester hydrochloride (6)** was prepared from L-isoleucine (30.0 g, 0.23 mol). The thick oil was triturated under Et_2O to give pure **6** (39.2 g, 94%) as a white hygroscopic solid, which had properties identical with those reported,[24] mp 82–85 °C, $[\alpha]^{29}_D$ = +25.0° (*c* = 2, H_2O) lit.[24] mp 99–100 °C, $[\alpha]^{22}_D$ = +27.2° (*c* = 2, H_2O)].

L-**Valine methyl ester hydrochloride (7)** was prepared as described above from L-valine (30.0 g, 0.24 mol). Recrystallization of the crude product (acetone) gave pure **7** (39.6 g, 98%) as a white solid, which had properties identical with commercial material,[12] mp 170–172 °C, $[\alpha]^{25}_D$ = +24.5° (*c* = 2, MeOH) [lit.[12] mp 171–173 °C, $[\alpha]^{21}_D$ = +23.6°].

Preparation of *N*-Chloroacetyl Derivatives of the Amino Acid Esters. The amino acid methyl ester hydrochloride, prepared as described above or purchased from Aldrich Chemical Co., was dissolved in a minimum amount of H_2O (pH 2). Then Na_2CO_3 was added until the pH became 10. The free amine was extracted from the H_2O layer with CH_2Cl_2 (5 times), dried, and concentrated in vacuo to ca. 50 mL. The amine was then added to a vessel containing Na_2CO_3 (1.05 equiv) under an atmosphere of dry N_2 gas. Chloroacetyl chloride (1.05 equiv) was added at once via a syringe. The mixture was allowed to stir at room temperature for 1 h and filtered, and the solvent was removed by rotary evaporation. The pure product was obtained after chromatography (silica, 60 g, CH_2Cl_2) followed by molecular distillation in a Kugelrohr apparatus.

L-***N*-(Chloroacetyl)glycine methyl ester (8)** was prepared as described above from glycine methyl ester hydrochloride (3.14 g, 25.0 mmol), Na_2CO_3 (2.78 g, 26.6 mmol), and $ClCH_2COCl$ (2.96 g, 26.2 mmol). Pure **8** was obtained after chromatography and molecular distillation as a colorless oil (2.10 g, 51%), which solidified on standing and had properties identical with those reported, bp 70–75 °C/0.05 Torr, mp 41–43 °C (lit.[14] bp 121–7 °C/0.1 Torr).[14] ^1H NMR: 3.73 (s, 3 H), 4.07 (s, 4 H), 7.23 (br s, 1 H).

L-***N*-(Chloroacetyl)alanine methyl ester (9)** was prepared as described above from **32** (2.00 g, 14.0 mmol), Na_2CO_3 (1.56 g, 14.7 mmol), and $ClCH_2COCl$ (1.66 g, 14.7 mmol). Pure **9** was obtained after chromatography and molecular distillation as a colorless oil (1.26 g, 50%), which solidified on standing, bp 65–70 °C/0.05 Torr, mp 34–35 °C, $[\alpha]^{25}_D$ = −50.5° (*c* = 2, MeOH). ^1H NMR: 1.47 (d, 3 H), 3.80 (s, 3 H), 4.07 (s, 2 H), 4.60 (m, 1 H), 7.00 (br s, 1 H). Anal. Calcd for $C_6H_{10}ClNO_3$: C, 40.12; H, 5.62. Found: C, 40.20; H, 5.62.

L-***N*-(Chloroacetyl)phenylalanine methyl ester (10)** was prepared as described above using **4** (4.10 g, 19.0 mmol), Na_2CO_3

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(2.12 g, 20.0 mmol), and $ClCH_2COCl$ (2.26 g, 20.0 mmol). Pure **10** was obtained after chromatography and molecular distillation as a colorless oil (4.71 g, 97%), which solidified upon standing and had properties identical with those reported,[15] bp 115–120 °C/0.05 Torr, mp 68–71 °C, $[\alpha]^{25}_D$ = +11.7° (c = 1, MeOH) [lit.[15] mp 68 °C, $[\alpha]_D$ = +6.0° (MeOH)]. ^1H NMR: 3.20 (d, 2 H), 3.74 (s, 3 H), 4.02 (s, 2 H), 4.94 (q, 1 H), 7.26 (br m, 6 H).

L-***N*-(Chloroacetyl)leucine methyl ester (11)** was prepared as described above from **5** (2.00 g, 11.0 mmol), Na_2CO_3 (1.22 g, 11.5 mmol), and $ClCH_2COCl$ (1.30 g, 11.5 mmol). Pure **11** was obtained after column chromatography followed by distillation (Kugelrohr) as a colorless oil (2.05 g, 84%), bp 80–85 °C/0.1 Torr, $[\alpha]^{25}_D$ = −27.7° (c = 2, MeOH). ^1H NMR: 1.04 (d, 6 H), 1.75 (m, 3 H), 3.80 (s, 3 H), 4.12 (s, 2 H), 4.73 (m, 1 H), 6.94 (br s, 1 H). IR: 3260, 2940, 1740, 1665, 1540, 1440, 1210, 1170, 1030, 990 cm^{-1}. Anal. Calcd for $C_9H_{16}ClNO_3$: C, 48.75; H, 7.29. Found: C, 48.61; H, 7.30.

L-***N*-(Chloroacetyl)isoleucine methyl ester (12)** was prepared as described above using **6** (2.00 g, 11.0 mmol), Na_2CO_3 (1.22 g, 11.5 mmol), and $ClCH_2COCl$ (1.30 g, 11.5 mmol). Pure **12** was obtained after chromatography and molecular distillation as a colorless oil (2.25 g, 92%), bp 65–70 °C/0.05 Torr, $[\alpha]^{25}_D$ = −7.9° (c = 2, MeOH). ^1H NMR: 0.93 (m, 6 H), 1.33 (m, 2 H), 1.93 (m, 1 H), 3.73 (s, 3 H), 4.07 (s, 2 H), 4.60 (m, 1 H), 7.00 (br s, 1 H). IR: 3270, 2930, 1740, 1665, 1530, 1440, 1210, 1155, 1020, 990 cm^{-1}. Anal. Calcd for $C_9H_{16}ClNO_3$: C, 48.75; H, 7.29. Found: C, 48.65; H, 7.25.

L-***N*-(Chloroacetyl)valine methyl ester (13)** was prepared as described above from **7** (5.00 g, 30.0 mmol), Na_2CO_3 (3.39 g, 32.0 mmol), and $ClCH_2COCl$ (3.61 g, 32.0 mmol). Pure **13** was obtained after column chromatography and subsequent molecular distillation as a colorless oil (5.17 g, 83%), which solidified upon standing and had properties identical with those reported,[13] bp 60–65 °C/0.05 Torr, mp 44–46 °C, $[\alpha]^{25}_D$ = −33.1° (c = 2.75, H_2O), $[\alpha]^{25}_D$ = −15.2° (c = 2, MeOH) [lit.[13] mp 45.8–46.6 °C, $[\alpha]^{25}_D$ = −37.8° (c = 2.75, H_2O)]. ^1H NMR: 0.93 (d, 6 H), 2.17 (m, 1 H), 3.73 (s, 3 H), 4.07 (s, 2 H), 4.48 (q, 1 H), 7.08 (br s, 1 H).

Preparation of the (Amino acid)aza-18-crown-6 Derivatives. A stirred solution of the parent aza-crown (0.53 g, 2.0 mmol) and the *N*-chloroacetyl amino acid ester (2.1 mmol) in MeCN (50 mL) containing Na_2CO_3 (0.23 g, 2.2 mmol) and NaI (0.31 g, 2.1 mmol) was heated to reflux under an atmosphere of N_2 for 5 h. The mixture was then allowed to cool and was filtered. The filtrate was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (100 mL) and the residual salts were filtered from the solvent. The solvent was then removed in vacuo. Purification involved chromatography of the crude product over a column of silica gel (30 g/g product, 5% $MeOH/CH_2Cl_2$ as eluent) to isolate the NaI complex. The complex was then dissolved in CH_2Cl_2 (150 mL), washed with H_2O (150 mL), and dried (Na_2SO_4). The pure product was obtained after recrystallization of the solid or chromatography of the oil through a short column of silica (10 g/1 g of product, 5% $MeOH/CH_2Cl_2$).

L-***N*-(*O*-Methylglycylglycyl)aza-18-crown-6 (14)** was prepared as described above using **8** (0.35 g). Pure **14** was obtained after recrystallization (Et_2O) as a white solid (0.45 g, 57%), mp 42–43 °C. ^1H NMR: 2.80 (t, 4 H), 3.27 (s, 2 H), 3.53 (m, 20 H), 3.70 (s, 3 H), 4.07 (d, 2 H), 8.23 (br s, 1 H). ^{13}C NMR: 39.05, 54.74, 56.82, 67.32, 68.52, 68.95, 168.84, 171.27. IR: 3340, 2880, 1740, 1675, 1540, 1460, 1350, 1210, 1110, 960, 840 cm^{-1}. Anal. Calcd for $C_{17}H_{32}N_2O_8$: C, 52.02; H, 8.23. Found: C, 51.83; H, 8.29.

L-***N*-(*O*-Methylisoleucylglycyl)aza-18-crown-6 (15)** was prepared as described above from **12** (0.47 g). Pure **15** was obtained after chromatography and subsequent Kugelrohr distillation as a pale yellow oil (0.45 g, 50%), bp 180–185 °C/0.05 Torr, $[\alpha]^{25}_D$ = −0.2° (c = 2, MeOH). ^1H NMR: 0.93 (d, 3 H), 1.28 (m, 6 H), 2.87 (t, 4 H), 3.23 (s, 2 H), 3.67 (m, 23 H), 4.73 (m, 1 H), 7.90 (br d, 1 H). ^{13}C NMR: 9.50, 13.58, 23.08, 35.37, 49.80, 52.88, 54.15, 57.43, 67.52, 68.26, 68.67, 68.81, 169.81, 170.21. IR: 3460, 3065, 2880, 1745, 1680, 1490, 1410, 1360, 1250, 1200, 1110, 950, 830 cm^{-1}. Anal. Calcd for $C_{21}H_{40}N_2O_8$: C, 56.22; H, 9.00. Found: C, 56.19; H, 9.03.

L-***N*-(*O*-Methylvalinylglycyl)aza-18-crown-6 (16)** was prepared as described above from **13** (0.44 g). Pure **16** was obtained after chromatography and subsequent Kugelrohr distillation as a pale yellow oil (0.49 g, 56%), bp 175–180 °C/0.05 Torr, $[\alpha]^{25}_D$ = −5.5° (c = 2, MeOH). ^1H NMR: 0.93 (d, 6 H), 2.20 (m, 1 H), 2.87 (t, 4 H), 3.27 (s, 2 H), 3.67 (m, 20 H), 3.73 (s, 3 H), 4.47 (m, 1 H), 7.93 (br d, 1 H). ^{13}C NMR: 16.15, 17.32, 28.96, 50.02, 53.06, 55.09, 57.59, 67.69, 68.44, 68.84, 170.10, 170.44. IR: 3440, 2880, 1740, 1675, 1580, 1470, 1360, 1270, 1220, 1110, 960, 840 cm^{-1}. Anal. Calcd for $C_{20}H_{38}N_2O_8$: C, 55.27; H, 8.83. Found: C, 55.35; H, 8.87.

***N*-[(Ethoxycarbonyl)methyl]aza-18-crown-6 (17).** Aza-18-crown-6 (0.53 g, 2.0 mmol), Na_2CO_3 (0.23 g, 2.2 mmol), CH_3CN (50 mL), and ethyl chloroacetate (0.26 g, 2.1 mmol) were stirred and heated to reflux for 12 h. The mixture was then cooled, filtered, and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (150 mL) and washed with H_2O (2 × 150 mL). After drying (Na_2SO_4), the CH_2Cl_2 was evaporated in vacuo. The residue was chromatographed over a column of alumina (60 g, 10% 2-PrOH/hexane), distilled in a Kugelrohr apparatus, and obtained as a colorless oil (0.55 g, 79%), bp 140–145 °C/0.1 Torr. ^1H NMR: 1.20 (t, 3 H), 2.90 (t, 4 H), 3.60 (m, 22 H), 4.13 (q, 2 H). ^{13}C NMR: 12.18, 51.99, 54.14, 57.90, 68.00, 68.20, 68.62, 169.59. IR: 2860, 1740, 1450, 1350, 1300, 1250, 1180, 1110, 1020, 980, 940, 830 cm^{-1}. Anal. Calcd for $C_{16}H_{31}NO_7$: C, 54.98; H, 8.96. Found: C, 54.87; H, 8.96.

Preparation of the (Amino acid)-4,13-diaza-18-crown-6 Derivatives. Diaza-18-crown-6 was obtained by hydrogenolysis (H_2, 10% Pd–C, absolute EtOH) of the corresponding *N,N'*-dibenzyl-4,13-diaza-18-crown-6 as previously described.[9] A stirred solution of the parent diaza-crown (0.53 g, 2.0 mmol) and the *N*-chloroacetyl amino acid ester (4.2 mmol) in MeCN (50 mL) containing Na_2CO_3 (0.47 g, 4.4 mmol) and NaI (0.63 g, 4.2 mmol) was heated to reflux under an atmosphere of N_2 for 12 h. The mixture was then allowed to cool and was filtered. The filtrate was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (100 mL) and the residual salts were filtered from the solvent. The solvent was then removed in vacuo. Purification involved preparative column chromatography of the crude product over a column of silica gel (30 g/g product, 5% $MeOH/CH_2Cl_2$ as eluent) to isolate the NaI complex. The complex was then dissolved in CH_2Cl_2 (150 mL), washed with H_2O (150 mL), and dried (Na_2SO_4). The pure product was obtained after recrystallization of the solid or chromatography of the oil through a short column of silica (10 g/1 g product, 5% $MeOH/CH_2Cl_2$).

L,L-***N,N'*-Bis(*O*-methylglycylglycyl)-4,13-diaza-18-crown-6 (18)** was prepared as described above using 0.66 g of the side-arm precursor. Pure **18** was obtained after recrystallization from THF as a white crystalline solid (0.60 g, 58%, mp 118–119 °C). ^1H NMR: 2.83 (t, 8 H), 3.50 (s, 16 H), 3.73 (s, 6 H), 4.08 (d, 4 H), 8.27 (br s, 2 H). ^{13}C NMR: 39.28, 49.95, 54.87, 56.05, 67.12, 68.72, 168.73, 170.92, 170.92. Anal. Calcd for $C_{22}H_{40}N_4O_{10}$: C, 50.75; H, 7.76; N, 10.76. Found: C, 50.78; H, 7.76; N, 10.72.

L,L-***N,N'*-Bis(*O*-methylalanylglycyl)-4,13-diaza-18-crown-6 (19)** was prepared as described above using 0.75 g of the side-arm precursor. Pure **19** was obtained as a white, crystalline solid (0.55 g, 50%, mp 62–63 °C, $[\alpha]^{25}_D$ = −19.3° (c = 2, MeOH) after recrystallization from ether. ^1H NMR: 1.47 (d, 6 H), 2.87 (t, 8 H), 3.25 (s, 4 H), 3.60 (m, 22 H), 4.40 (m, 2 H), 8.00 (br d, 2 H). ^{13}C NMR: 15.87, 45.59, 50.19, 53.43, 57.31, 67.45, 68.66, 169.62, 171.26. IR (Nujol): 3350, 2920, 2880, 1750, 1670, 1530, 1510, 1380, 1300, 1280, 1240, 1120, 1090, 1050, 930 cm^{-1}. Anal. Calcd for $C_{24}H_{44}N_4O_{10}$: C, 52.53; H, 8.10. Found: C, 52.44; H, 8.13.

Preparation of L,L-*N,N'*-Bis(*O*-methylphenylalanylglycyl)-4,13-diaza-18-crown-6 methyl ester (20) was prepared as described above from **10** (1.07 g) and isolated as its NaI complex. Pure **20**·NaI was crystallized from $CHCl_3$/hexane (ca. 1:1). Washing with THF gave a white solid (1.43 g, 84%), mp 183–184 °C, $[\alpha]^{25}_D$ = −7.1° (c = 2, MeOH). ^1H NMR: 2.63 (t, 8 H), 3.12 (d, 4 H), 3.40 (m, 20 H), 3.60 (s, 6 H), 4.70 (m, 2 H), 7.20 (s, 10 H), 7.45 (br d, 2 H). ^{13}C NMR: 35.29, 50.33, 52.42, 56.49, 64.98, 66.63, 124.78, 126.39, 127.44, 134.78, 169.76, 169.94. IR (Nujol): 3640, 3480, 3240, 3220, 2920, 2860, 1740, 1685, 1540, 1470, 1285, 1240, 1120, 1090, 930, 750, 700 cm^{-1}. Anal. Calcd for $C_{36}H_{52}N_4O_{10}$·NaI: C, 50.82; H, 6.17. Found: C, 50.71; H, 6.21. The complex was washed with water to afford **20** as a pale yellow oil after chromatography (0.91 g, 65%) and was characterized as its NaI complex (above), $[\alpha]^{25}_D$ = −1.75°.

L,L-***N,N'*-Bis(*O*-methylleucylglycyl)-4,13-diaza-18-crown-6

Table VII. Crystal Data and Data Collection Parameters

	$C_{22}H_{40}N_4O_{10}$	$C_{22}H_{40}N_4O_{10}KI$	$C_{22}H_{40}O_{10}NaI \cdot {}^1/_2C_4H_80.{}^1/_2H_2O$
fw	520.6	686.6	715.6
cryst system	triclinic	monoclinic	monoclinic
space group	$P\bar{1}$	$C2/c$	$P2_1/c$
a, Å	9.0210 (8)	15.656 (4)	9.732 (3)
b, Å	10.4768 (15)	14.752 (3)	17.710 (2)
c, Å	15.357 (2)	26.784 (3)	38.848 (3)
α, deg	87.457 (12)		
β, deg	87.119 (10)	90.01 (2)	96.99 (2)
γ, deg	68.042 (9)		
V, Å^3	1343.9 (4)	6186 (4)	6646 (4)
Z	2	8	8
D_t, g cm^{-3}	1.286	1.474	1.430
T, deg	19	20	26
μ, cm^{-1}	0.95	12.08	10.18
$F(000)$	560	2816	3048
cryst size, mm	0.48 × 0.48 × 0.70	0.24 × 0.32 × 0.36	0.32 × 0.36 × 0.48
θ limits, deg	1–26	1–25	1–23
scan rates, deg·min^{-1}	0.64–4.0	0.80–4.0	0.90–4.0
precision, $I/\sigma(I)$	25	25	25
max scan time, s	90	90	60
min rel abs coeff, %		89.84	94.22
unique data	5251	5443	9234
observed data	4034	2595	5512
variables	486	347	714
B for H atoms, Å^2	refined	6.0	5.0
R(all data)	0.059	0.128	0.099
R	0.041	0.035	0.041
R_W	0.054	0.034	0.048
GOF	2.702	1.369	1.813
max residual, e Å^{-3}	0.34	0.51	0.69

(**21**) was prepared as described above from **11** (0.93 g) and obtained as its NaI complex. The complex was chromatographed and triturated with Et_2O. Crystallization from THF/ether gave pure **21**·NaI as a white crystalline solid (1.13 g, 72%), mp 104–105 °C, $[\alpha]^{25}_D = -36.2°$ (c = 2, MeOH). ^{1}H NMR: 0.93 (d, 12 H), 1.67 (m, 6 H), 2.80 (t, 8 H), 3.53 (m, 20 H), 3.68 (s, 6 H), 4.40 (m, 2 H), 7.53 (br d, 2 H). ^{13}C NMR: 19.86, 20.83, 22.90, 38.22, 49.68, 50.28, 52.16, 56.33, 65.17, 66.83, 170.16, 171.44. IR (Nujol): 3620, 3480, 3200, 2945, 2920, 1740, 1670, 1550, 1525, 1460, 1370, 1280, 1190, 1100, 815 cm^{-1}. Anal. Calcd for $C_{30}H_{56}N_4O_{10}$·NaI: C, 46.03; H, 7.22. Found: C, 45.64; H, 7.18. Pure **21** was isolated, after washing and chromatography, as a pale yellow crystalline solid (0.65 g, 51%), which was recrystallized from ether, mp 72–73 °C, $[\alpha]^{25}_D = -15.8°$ (c = 2, MeOH). ^{1}H NMR: 0.93 (d, 12 H), 1.60 (m, 6 H), 2.80 (t, 8 H), 3.13 (s, 4 H), 3.62 (m, 22 H), 4.53 (m, 2 H), 7.88 (br d, 2 H). ^{13}C NMR: 19.93, 21.04, 23.01, 39.23, 48.33, 50.12, 53.21, 57.37, 67.54, 68.80, 169.74, 171.36. IR (Nujol): 3320, 2940, 2860, 1740, 1680, 1530, 1470, 1380, 1300, 1250, 1220, 1150, 1110, 990 cm^{-1}. Anal. Calcd for $C_{30}H_{56}N_4O_{10}$: C, 56.93; H, 8.94. Found: C, 56.79; H, 8.98.

L,L-***N,N'*-Bis(*O*-methylisoleucylglycyl)-4,13-diaza-18-crown-6 (22)** was prepared as described above from **12** (0.93 g) and obtained as its NaI complex. The complex was chromatographed and triturated with Et_2O. Crystallization from THF/ether gave pure **22**·NaI as a white crystalline solid (0.95 g, 61%), mp 120–121 °C, $[\alpha]^{25}_D = -19.4$ (c = 2, MeOH). ^{1}H NMR: 0.93 (m, 12 H), 1.47 (m, 6 H), 2.80 (t, 8 H), 3.53 (m, 20 H), 3.67 (s, 6 H), 4.27 (m, 2 H), 7.40 (br d, 2 H). ^{13}C NMR: 9.46, 13.77, 23.66, 34.62, 50.02, 52.21, 55.58, 56.48, 65.16, 66.83, 170.25. IR (Nujol): 3620, 3460, 3240, 2920, 2840, 1740, 1670, 1530, 1460, 1190, 1100, 930 cm^{-1}. Anal. Calcd for $C_{30}H_{56}N_4O_{10}$·NaI: C, 46.03; H, 7.22. Found: C, 45.60; H, 7.17. Pure **22** was obtained after washing (H_2O) and chromatography (silica) as a pale yellow oil (0.78 g, 60%), $[\alpha]^{25}_D = -3.1°$ (c = 2, MeOH). ^{1}H NMR: 1.30 (m, 18 H), 2.87 (t, 8 H), 3.22 (s, 4 H), 3.60 (m, 16 H), 3.70 (s, 6 H), 4.57 (m, 2 H), 7.93 (br d, 2 H). ^{13}C NMR: 9.64, 13.70, 23.22, 35.66, 49.93, 53.02, 54.21, 57.63, 67.72, 68.90, 169.75, 170.37. IR: 3340, 2960, 2880, 1745, 1675, 1510, 1460, 1355, 11260, 11200, 1120, 935, 820 cm^{-1}. Anal. Calcd for $C_{30}H_{56}N_4O_{10}$·H_2O: C, 55.35; H, 9.00. Found: C, 55.54; H, 8.77.

L,L-***N,N'*-Bis(*O*-methylvalinylglycyl)-4,13-diaza-18-crown-6 (23)** was prepared as described above from **13** (0.87 g). Pure **23** was obtained after chromatography as a pale yellow oil (0.71 g, 59%), $[\alpha]^{25}_D = -3.25°$ (c = 2, MeOH). ^{1}H NMR: 1.06 (d, 12 H), 2.41 (m, 2 H), 2.91 (t, 8 H), 3.30 (s, 4 H), 3.69 (m, 22 H), 4.45 (q, 2 H), 7.36 (br d, 2 H). ^{13}C NMR: 16.14, 17.38, 29.16, 50.13, 53.15, 55.09, 57.69, 67.81, 69.00, 170.04, 170.54.

***N,N'*-Bis(*n*-propyl)-4,13-diaza-18-crown-6 (24)** was prepared as described by alkylation of 4,13-diaza-18-crown-6 as previously described.[9d]

***N,N'*-Bis(carbomethoxymethyl)-4,13-diaza-18-crown-6 (25)** was prepared by the single-step BiBLE synthesis previously described.[9a]

X-ray Data Collection and Structure Solution. Intensity data were collected on an Enraf-Nonius CAD4 diffractometer equipped with Mo K_α radiation (λ = 0.71073 Å) and a graphite monochromator, by ω–2θ scans designed to yield equal relative precision for all observed data, subject to a maximum scan time. Cell dimensions were obtained from a least-squares fit to the setting angles of 25 reflections having $13.0° < \theta < 14.0°$ for the uncomplexed molecule and setting angles of 25 reflections having $12.0° < \theta < 13.0°$ for the sodium complex and the potassium complex. One hemisphere of data was collected for all the crystal structures; angular limits and other experimental parameters are listed in Table VII. Data reduction included corrections for background, Lorentz, and polarization effects. Absorption effects were insignificant. Data having $I > 3\sigma(I)$ were considered observed and used in the refinement.

The structures were solved by direct methods using MULTAN[25] and refined by full-matrix least squares based on F with weights $\omega = \rho^{-2}$, using the Enraf-Nonius SDP.[26] Scattering factors were those of Cromer[27] with anomalous coefficients of Cromer and Waber.[28] Non-hydrogen atoms were treated anisotropically. Hydrogen atoms were located by difference maps and included as fixed contributions. Final R factors and residual electron density are given in Table VII.

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Registry No. 3·HCl, 2491-20-5; 4·HCl, 7524-50-7; 5·HCl, 7517-19-3; 6·HCl, 18598-74-8; 7·HCl, 6306-52-1; 8, 76969-81-8; 9, 118375-95-4; 10, 2537-00-0; 11, 102115-71-9; 12, 102115-69-5; 13, 1492-16-6; 14, 113306-72-2; 15, 113306-74-4; 16, 113306-73-3; 17, 113306-71-1; 18, 118375-96-5; 18·KI complex, 113159-91-4; 18·NaI complex, 118398-03-1; 19, 118375-97-6; 20, 118375-98-7; 20·NaI complex, 118376-03-7; 21, 118375-99-8; 21·NaI complex, 118376-04-8; 22, 118376-00-4; 22·NaI complex, 118398-02-0; 23, 118376-01-5; 24, 77112-68-6; 25, 118376-02-6; 26, 72912-00-6; H-Gly-OMe·HCl, 5680-79-5; $ClCH_2COCl$, 79-04-9; $ClCH_2COOEt$, 105-39-5; Na, 7440-23-5; K, 7440-09-7; aza-18-crown-6, 33941-15-0; 4,13-diaza-18-crown-6, 23978-55-4.

Supplementary Material Available: Atomic coordinates, thermal parameters, distances, and angles for 18, 18·NaI complex, and 18·KI complex (25 pages). Ordering information is given on any current masthead page.

Oxidation of Alkynes Catalyzed by Mo(VI) and W(VI) Polyoxometalates

Francesco Paolo Ballistreri, Salvatore Failla, Emanuela Spina, and Gaetano Andrea Tomaselli*

Dipartimento Scienze Chimiche, University of Catania, Viale A. Doria 6, 95125 Catania, Italy

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Oxidation of alkynes, both terminal and internal, is performed by hydrogen peroxide in the presence of catalytic amounts of (cetylpyridinium)$_3PM_{12}O_{40}$ (M = Mo(VI), W(VI)). A comparison with the analogous oxidation reactions catalyzed by Na_2MO_4 reveals that $PM_{12}O_{40}^{3-}$ anions are more efficient catalysts than MO_4^{2-} in the oxidation of terminal alkynes to carboxylic acids. The higher catalytic activity of peroxometalates allows the oxidation of internal alkynes by hydrogen peroxide, which does not occur with MO_4^{2-} salts.

Owing to the rapid developments of phase-transfer procedures, the catalyzed oxidations by hydrogen peroxide find increasing synthetic applications.[1-6] Basically, the procedures involve the formation of a peroxometal complex in the aqueous phase via addition of hydrogen peroxide to the metal derivatives and the transfer, by a suitable phase-transfer agent, of the peroxidic species into an organic phase containing the substrate.

In most of the reported studies the metal precursor is a salt of general formula Na_2MO_4 (M = Mo(VI) or W(VI)) dissolved in fairly acidic aqueous solutions. It is well known that, under these conditions, upon addition of hydrogen peroxide an oxodiperoxomolybdenum or -tungsten complex is formed of general formula $MO(O_2)_2$, which represents the real oxidant species.[5] Recently, however, the attention has been focused on heteropolyacids such as $H_3PM_{12}O_{40}$,[7-9] which also add hydrogen peroxide to form peroxometal species, whose structure is not yet well characterized.

Although quantitative data are lacking in the literature, there is some evidence that peroxo complexes formed from heteropolyacids may be more effective than those formed from simple anions in the oxidation of alkenes and alcohols.[7-9] Recently we turned our attention to the oxidation of acetylenic compounds observing that such substrates, usually rather reluctant to undergo oxidative reactions, are easily oxidized by peroxomolybdenum or peroxotungsten complexes.[5,6,10] However, the presence of a mercuric salt as cocatalyst is a necessary requisite. Therefore, it was of some interest to ascertain whether, also in alkyne oxidations, peroxometal complexes derived from heteropolyacids could behave as effective oxidants as compared with simple peroxometal species. Moreover, the need of the presence of the mercuric salt, which may have some interactions with heteropolyacids, makes it difficult to predict the behavior of the oxidations.

Results and Discussion

The results, collected in Table I, provide some useful information on the general features of the alkynes oxidation by peroxo species formed from heteropolyacids. The data reported have been obtained by using as precursor tris(cetylpyridinium) 12-molybdophosphate or 12-tungstophosphate (CMP or CWP) and $Hg(CF_3CO_2)_2$ as cocatalyst. Details on the reaction conditions are provided in Table I. As model substrates, we have used four alkynes where the triple bonds, either internal or terminal, carry both alkyl or aryl substituents. For comparison purposes, Table I collects also the data referring to the oxidation of the same or similar substrates when H_2MO_4 (obtained from $Na_2MO_4 \cdot 2H_2O$ and H_2SO_4) is the precursor of the peroxo species. In this case, the phase-transfer agent is a quaternary ammonium salt (Aliquat)[5,6] or a neutral ligand (hexaethylphosphoric triamide, HEPT).

Inspection of the data of Table I immediately reveals that indeed the peroxo complexes derived from CMP or CWP are remarkably more reactive than usual peroxomolybdenum or peroxotungsten complexes, $MO(O_2)_2$, as

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