Tetrahedron Letters,Vol.28,No.16,pp 1749-1752,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

ONE- AND TWO-ARMED LARIAT ETHER PEPTIDE DERIVATIVES: SYNTHESES AND CATION BINDING PROPERTIES

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Abstract. Series of peptide-based lariat ethers derived from aza-18-crown-6 and bibracchial lariat ethers (BiBLEs) based on 4,13-diaza-18-crown-6 have been prepared. Sidearms incorporate inter alia the amino acids glycine, alanine, phenylalanine, leucine, isoleucine, and valine. Cation binding affinities for Na^+ and K^+ are reported.

Our interest in the structure and binding behavior of valinomycin[1] led us to study the class of compounds we call lariat ethers. This family of compounds has now grown to include single-armed species having arms attached at carbon (i.e. carbon-pivot lariat ethers),[2] arms attached at nitrogen (i.e. nitrogen-pivot LEs),[3] and two-armed systems (bibracchial lariat ethers, BiBLEs) in which the arms are so far attached to nitrogen.[4,5] Bibracchial lariat ethers having peptide sidearms are particularly attractive synthetic targets because they are virtually unknown and have multiple potential applications. They present both amide and ester donors in the sidearm to a ring-bound cation and it is interesting to ask which, if either, of these donors will be favored by cations. Further, our long term goal of constructing model cation channels makes essential an understanding of peptide sidearms since these may be used to connect macrorings. Variation in amino acid units offers the opportunity to independently alter both lipophilicity and rigidity in the sidearms while maintaining the same distance relationships.

The decision was made to base the studies on the 18-membered ring compounds since aza-18-crown-6, diaza-18-crown-6, and triaza-18-crown-6 are all synthetically accessible. Those compounds having a single sidearm would derive from aza-18-crown-6, **1**,[6] and those having two arms would be based on 4,13-diaza-18-crown-6, **2**. The synthetic scheme envisioned was simple: the secondary amine, either **1** or **2**, would be alkylated using an appropriate glycine derivative. This derivative would then be coupled to afford a dipeptide crown of the form >N-gly-amino acid. Model studies on aza-15-crown-5,

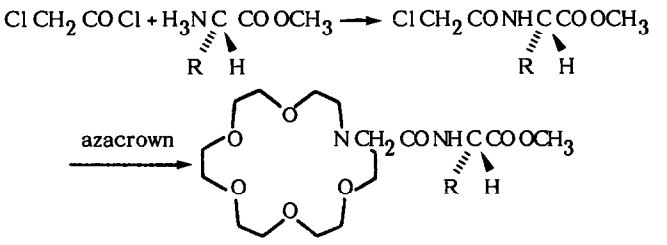
Table. Syntheses and Cation Binding Properties of Peptide-derived Lariat Ethers and BiBLEs

Cpd. No.	Sidearm[a]		Percent Yield	MP or (bp)[b] °C	Rot'n[c,d] $[\alpha]_D$	log K_S in MeOH[c] Na^+	K^+
Aza-18-crown-6 derivatives							
4	$CH_2CH_2CH_3$	n-propyl	19	(140-145)	---	3.50	4.92
5	CH_2-CO-OCH_2CH_3	gly-OEt	79	(140-145)	---	4.67	5.92
6	CH_2-CO-NH-CH_2-CO-OCH_3	gly-gly-OMe	51	42-43	---	3.50	4.53
7	CH_2-CO-NH-CH(i-Pr)-CO-OCH_3	gly-val-OMe	56	(175-180)	-5.5	4.04	5.03
8	CH_2-CO-NH-CH(s-Bu)-CO-OCH_3	gly-ile-OMe	50	(180-185)	-0.2	4.03	5.10
4,13-Diaza-18-crown-6 derivatives							
9	$CH_2CH_2CH_3$	n-propyl	78[e,f]	(130-1/.06)	---	2.86	3.78
10	CH_2-CO-OCH_2CH_3	gly-OEt	92[g]	(195-7/.02)	---	5.51	5.78
11	CH_2-CO-NH-CH_2-CO-OCH_3	gly-gly-OMe	58	118-119	---	3.35	3.32
12	CH_2-CO-NH-CH(Me)-CO-OCH_3	gly-ala-OMe	50	62-63	-19.3	4.36	4.21
13	CH_2-CO-NH-CH(i-Bu)-CO-OCH_3	gly-leu-OMe	51	72-73	-15.8	4.26	4.17
14	CH_2-CO-NH-CH(s-Bu)-CO-OCH_3	gly-ile-OMe	60	oil[h]	-3.1	4.16	4.09
15	CH_2-CO-NH-CH(i-Pr)-CO-OCH_3	gly-val-OMe	59	oil[h]	-3.25	4.18	4.11

Notes a. Attached at the macroring nitrogen atom(s); all chiral centers have the L configuration. b. boiling point at 0.05 torr except for compound **4**, at 0.6 torr. c. at 25 °C. d. c=2, methanol. e. Obtained by acylation of 4,13-diaza-18-crown-6. f. First e (above) then reduction. g. Obtained by alkylation of diaza-18-crown-6. h. Isolated by column chromatography.

3, proved disappointing. Several attempts to prepare aza-15-crown-5 amino acid derivatives using coupling methods (DCC,[7] mixed anhydride[8]) between N-carboxymethylaza-15-crown-5 and L-valine methyl ester hydrochloride were unsuccessful. In our hands, the mixed anhydride method afforded low yields and products were difficult to purify when DCC was used as the coupling agent.

The successful strategy used to prepare the desired lariat ethers involved two steps. First, amino acid methyl ester HCl salts were converted into their N-chloroacetyl derivatives. The N-substituted aza-18-crown-6 derivatives were then obtained by N-alkylation. The approach is illustrated in Scheme 1 and the results are recorded in the Table.



The optical rotations recorded in the Table are for isolated materials which are chemically pure. Since none of these compounds had previously been reported, we attempted to assess the extent of racemization, if any, by the following experiments. The sidearm precursor to **7** was maintained under the reaction conditions in the absence of NaI and using N-methylmorpholine instead of a 2°-azacrown. The rotation decreased approximately 10% during the course of the reaction. We also subjected azacrown **7** to the alkylation reaction conditions with a loss of optical activity of less than 10%. It is therefore likely that some enantiomeric material is present in each azacrown having one or more chiral sidearms, but the amount is apparently less than 10%.

The cation binding profiles[9] for these compounds are found in the two righthand columns of the Table. The N-propyl derivatives (**4** and **9**) are included along with the glycine ester derivatives (**5** and **10**) for comparative purposes. It is interesting to note that Na^+ cation binding for both one- and two-armed gly-gly-OMe derivatives (**6** and **11**) are the lowest in each group. The same is true for the K^+ cation binding although its K^+ affinity for **6** is significantly higher than for Na^+. In the single-armed series, K^+-binding strengths exceed the Na^+-binding affinities as expected.[10] This selectivity is not observed for the dipeptide BiBLEs. In all cases (**11**-**15**), log K_S for either Na^+ or K^+ with these compounds is the same or nearly so.

Attempting to account for differences in cation binding strengths and selectivities in molecules such as these is a perilous business because the relative contributions of enthalpy and entropy to K_S are not known from the latter value alone. Some general comparisons are in order, however. Both series of molecules are derivatives of 18-crown-6 which exhibits the following log K_S values in

anhydrous MeOH at 25 °C: Na^+, 4.34; K^+, 6.08.[10] Substitution of the >N-propyl unit for a single ring-oxygen reduces the binding to 3.50 and 4.92 respectively. Replacement of two oxygen atoms by >N-propyl groups diminishes the binding to 2.86 and 3.78. The reduction in Na^+-binding strength is 0.84 log units for the first replacement of N and 0.64 for the second. The K^+-binding strength diminishes by 1.16 and 1.14 log units for successive replacements of O by N. This is expected since nitrogen is a poorer donor for alkali metal cations than is oxygen. The loss of macroring ether oxygen atoms is compensated by the presence of carbonyl donor groups present in the sidearms. The sidearm donors also compensate for the loss of solvation which is present in simple macrocyclic complexes such as form with 18-crown-6. Although the involvement of both oxygen donors in cation binding appears possible from an examination of molecular models, the crystal structure shown in the accompanying paper[11] belies this conclusion. It thus appears that the loss of ring-oxygen atoms is more costly than can be compensated by the relatively rigid, albeit polar, dipeptide sidearms.

Since the sidearms are relatively rigid and since only the first carbonyl groups are oriented inward, a relatively rigid cavity is produced. We would therefore have predicted a substantial selectivity for K^+ over Na^+ but this is observed only for the single-armed compounds, **4-8.** For a discussion of the interactions in binding observed for the K^+ complexes of **8** compared to the free ligand, please see the following Letter.

Acknowledgments. We warmly thank the NIH for grants (GM-29150, GM-31846, GM-36262) which supported this work.

Notes and References

1. Brockmann, H.; Schmidt-Kastner, G.; Chem. Ber. **1955,** 88, 57.
2. (a) Gokel, G.W.; Dishong, D.M.; Diamond, C.J.; J. Chem. Soc. Chem. Commun. **1980,** 1053.
   (b) Dishong, D.M.; Diamond, C.J.; Cinoman, M.I.; Gokel, G.W.; J. Am. Chem. Soc. **1983,** 105, 586.
3. Schultz, R.A.; White, B.D.; Dishong, D.M.; Arnold, K.A.; Gokel, G.W.; J. Am. Chem. Soc. **1985,** 107, 6659-6668.
4. (a) Gatto, V.J.; Gokel, G.W.; J. Am. Chem. Soc., **1984,** 106, 8240-8244.
   (b) Gokel, G.W.; Gatto, V.J.; United States Patent Number 4,597,903, July 1, 1986.
5. Gatto, V.J.; Arnold, K.A.; Viscariello, A.M.; Miller, S.R.; Gokel, G.W.; J. Org. Chem. **1987,** in press.
6. Gokel, G.W.; Garcia, B.J.; Tetrahedron Letters, **1977,** 317.
7. Schultz, R.A.; Ph.D. Thesis, University of Maryland, 1984.
8. (a) Merrifield, R.B.; Mitchell, A.R.; Clarke, J.E.; J. Org. Chem. **1974,** 39, 660.
   (b) Vaughn, J.R.; Osato, R.L.; J. Am. Chem. Soc. **1952,** 74, 676.
9. Arnold, K.A.; Gokel, G.W.; J. Org. Chem. **1986,** in press.
10. Gokel G.W.; Goli, D.M.; Minganti, C.; Echegoyen, L.; J. Am. Chem. Soc., **1983,** 105, 6786.
11. White, B.D.; Fronczek, F.R.; Gandour, R.D.; Gokel, G.W.; Tetrahedron Lett., **1987,** following Letter.

(Received in USA 11 November 1986)