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MOLECULAR CONFORMATION OF ERABUTOXIN b; ATOMIC COORDINATES AT 2.5 Å RESOLUTION M. R. Kimball, A. Sato*, J. S. Richardson**, L. S. Rosen, and B. W. Low[†] Department of Biochemistry, Columbia University, 630 W. 168 St., N.Y., N.Y. 10032

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SUMMARY: Atomic coordinates determined from a 2.5 Å electron density map are given for erabutoxin b, a sea snake venom postsynaptic neurotoxin. The principal structural features, anti-parallel β pleated sheet, β bulge and β bends are described. The erabutoxin b structure is discussed as structural prototype of this class of homologous curare-mimetic neurotoxins from both land and sea snakes.

In this communication we provide atomic coordinates for erabutoxin b, a sea snake venom neurotoxin, based on a 2.5 Å electron density map and describe major features of the molecular conformation and stereochemistry of this single chain protein (M_r 6861) considered as prototype for a whole class of neurotoxins. Erabutoxin b, from the sea snake <u>Laticauda semifasciata</u>, is one of nearly 50 homologous neurotoxins from both land (elapid) and sea (hydrophid) snake venoms which bind to the cholinergic receptor at the postsynaptic membrane and block neuromuscular transmission in a nondepolarizing curaremimetic mode.

The main structural features of this short chain toxin observed at a lower resolution were described earlier, and a preliminary discussion of the distribution of some common invariant and conservatively-substituted⁺ residues given (1). The significance of the erabutoxin b structure as prototype was recognized and a reactive site region described (1,2). There are two toxin series, short with 60÷62 and long with 71÷74 residues, with 18 invariant and 7 conservatively-substituted positions in common, which include four invariant disulfide linkages. These latter play a unique and evident struc-

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^{*}Conservative substitution is used here to define conservation of residue type, i.e., Ser/Thr-hydroxyl group, Glu/Asp-carboxyl group, Val/Leu/Arg-hydrophobic group and Tyr/His/Trp-aromatic group.

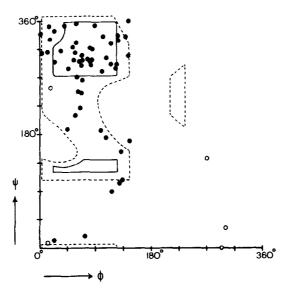


Fig. 1. Ramachandran angle plot for erabutoxin b showing "fully allowed" (——) and "outer limit" (---) boundaries. [O] Gly; [●] Other residues.

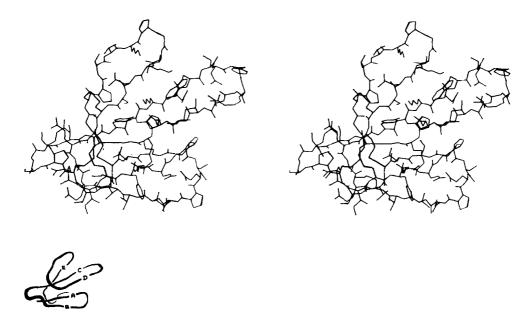


Fig. 2. Stereo drawing of erabutoxin b structure showing all the residues, produced by the GRIP-75 Molecular Graphics System.

tural role; both native conformation and toxicity are lost completely when they are reduced (3).

TABLE 1 Atomic Coordinates for Erabutoxin b.

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N 265 93 226 19 SER C 261 207 CA 290 60 224 N 43 96 126 C 254 217		CA 257 155 224
CB 302 80 217 CA 40 91 113		CB 265 151 211
OG 312 86 225 CB 25 91 108		CG2 256 154 195
C 287 69 235 OG 16 93 119		CG1 278 158 208
O 295 60 236 C 48 97 102 O 50 91 91		CD1 288 156 219 C 244 147 224

Atomic coordinates are in Angstroms (x 10) measured along the 3 principal axes a.b and c of the orthorhombic cell (1).

TABLE 1 (continued)

	lox lo	Y 16	ı	10x 10y 102			10x 10Y 10Z			10x 10x 102					
38	GLU			С	149	227	176	51	LYS			57	SER		
N	234	154	223	ō	161	230	173	N	236	244	204	N	177	117	6
CA	220	148	223	-				CA	234	244	189	CA	183	106	- 6
ČB	210	156	231	45	THR			CB	247	247	182	CB	197	110	•
CG	200	146	235	à.	138	234	177	ČĞ	258	240	188	OG	200	103	- 4
CD	191	153	243	ĈΑ	137	249	176	ão	271	243	161	č	185	95	7
OE1	103	162	237	ČB	126	254	185	ČĒ	263	236	187	ŏ	190	98	ė
		151		CG2	121	244	195	N2	296	240	181	-			•
OE 2	189		256	OG1	131	265	193	Ĉ	227	232	183	58	GLU		
Ç	215	146	208		150	255	182	č	224	222	189	N	162	83	6
0	213	155	201	C				U	224	242	107	CA	179	73	7
				0	154	251	193					CB	174	58	í
39	ARG								LEU	222	340	CG	159	51	1
N	214	133	206	46	VAL			N.	225	233	169				
CA	208	128	193	N	157	263	175	CA	216	223	162	CD	145	60	1
CB	215	114	189	CA	170	268	179	ÇВ	204	221	167	OE1	146	72	7
CG	230	114	191	CB.	175	278	168	ÇĞ	193	229	159	OE2	133	55	
CD	237	108	179	CC1	189	283	172	CD1	182	220	153	c	169	73	. 5
NE	251	106	182	CG2	177	271	154	CD3	185	239	167	0	186	77	10
CZ	256	106	194	c	169	274	193	c	221	222	147				
NEH.		106	197	0	159	276	198	٥	219	231	139	59	VAL		
NEH.		113	204									N	202	69	8
c	193	124	196	47	LYS			53	SER			CA	211	70	10
ŏ	190	119	207	N	182	273	199	N	227	210	144	СВ	209	58	10
•				CA	184	275	213	CA	228	203	131	CGl	208	61	12
40	GLY			CB	177	264	220	CB	243	198	130	CG2	198	49	10
N	186	128	186	ČĞ	172	269	232	ŌĞ	246	198	116	С	222	80	9
	171	126	186	CD	166	258	239	č	218	192	130	Ó	232	75	g
ÇV	165	128	173	ČE	161	263	252	č	215	185	139	_			
Ç				N2	156	252	260	•	•••			60	CSS		
O	172	129	163	c.	195	281	216	54	CSS			N	220	92	3.0
								N N	210	195	117	ĈA	228	103	- 9
	CSS			o	206	277	211				117	CB	219	113	i
N	152	128	172					CA	198	185	114	SG.	201	118	9
CA	143	130	160	48	PRO			CB	164	192	115	Č.	233	111	10
CB	130	123	158	N	196	293	226	SG	179	199	132	ŏ	233	123	16
SG	127	105	162	CD	184	298	232	Ç	199	178	101	U	231	123	1,
С	138	144	157	CA	208	301	229	o	202	183	91				
С	131	150	166	CB	204	312	238					61	ASN		
				CC	189	310	240		CSS			N	231	107	11
42	GLY			С	220	293	234	N	196	165	103	CA	230	112	13
N	141	151	146	0	219	287	245	CA	197	155	93	СВ	220	106	1:
CA	134	164	143					CB	208	147	92	CG	205	114	13
č	143	176	144	49	GLY			SG	205	134	103	OD1	196	111	13
ò	154	176	147	N		293	225	Ċ	186	145	88	ND2		125	14
-				CA	243		227	ō	176	138	96	С		109	10
43	CSS			č	243	272	225					0	242	100	14
N	137	188	141	ŏ	253	267	220	56	GLU						
CA	145	200	142	-				Ñ		145	76	62	ASN		
	149	206	128	50	ILE			CA	170	140		N	254	115	1:
CB				N	232	266	229	ČB.	164	150	59	ČA	266	114	14
5G	164	215	128	ČA.	230	251	227	CG	160	162	65	CB	275	104	1:
ç	141	206	154					CD	154	172	55	ČĞ	268	95	12
o	132	217	152	CB	218	246	235	0.61	149	183	60	OD1	269	96	ii
				CG2		256	245			170	43	ND2		85	i
44	PRO			CG1		243	226	OE 2	153			C	273	128	i
N	147	205	165	CDI		231	217	c	173	128	59	ŏ			
CD	155	193	166	c	227	249	212	0	174	131	46	U	266	138	14
ÇA	145	212	177	0	215	251	208								
CB	153	204	187												
CG	159	192	180												

Molecular Conformation. Atomic coordinates for the 2.5 Å structure are given in Table 1. The Ramachandran angle plot (4) and a stereo drawing of the structure based on the coordinates are shown in Figs. 1 and 2 respectively. These results were obtained using the GRIP-75 Molecular Graphics System build by the University of North Carolina, Department of Computer Science. Fitting of the molecular model to the electron density map and idealization procedures were employed in an iterative mode to be described elsewhere. In the Ramachandran plot (Fig. 1), apart from the less restrained Gly angles, most residues fall within the outer limit boundary shown and all others are within at least 22° of this region. The three principal molecular lobes may



Fig. 3. Erabutoxin b. Freehand sketch of alpha-carbon backbone model. The double broken lines indicate disulfide bridges.

be seen to emerge in Fig. 2 from the central invariant disulfide core. These curved lobes, bounded by Cys3 and Cys17, Cys24 and Cys41 (K*45), and by Cys43 and Cys54 (K49, K61) are formed by the five BADCE strands of the dominant antiparallel β structure (see inset) as well as by the outer rim segment 43-48 (K49-K55).

Fig. 3 shows the molecular shape in a view which emphasizes the curved shell-like concavity, and shows the protruding curled tongue of the long central DC lobe and the underlying "stand" formed by the C-terminal six-membered ring and 2 residue tail. In the short chain toxin series only the tapered neck region, Cys17-Cys24 (compare Fig. 4), is of variable length; all other molecular segments are invariant in length.

The erabutoxin b molecule is open, much of it only one peptide chain thick. Apart from a very few residues in the region around the disulfide core there are no buried residues or regions of backbone chain inaccessible to solvent. Nonetheless a striking degree of cross-linking maintains molecular stereochemistry. This includes not only hydrogen bonds between main-chain atoms in the β structure and elsewhere, but also numerous other main-chain and sidechain crosslinking interactions. Because of these interactions, the upper concave molecular surface (facing the viewer in Fig. 4) formed by the three *The sequence enumerations used are that of erabutoxin b and, where different, that of Karlsson (K) which orders all sequence alignments to preserve

maximum homology in both short and long chain series.

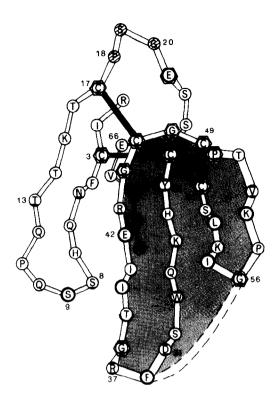


Fig. 4. View (partially schematic) of the erabutoxin b molecule looking into the concavity. The reactive site is shown shaded. One-letter residue code and Karlsson sequence enumeration used.

- Invariant position in both long and short chain toxins; in short chain toxins only \bigcirc .
- Conservatively substituted position in both long and short chain toxins; in short chain toxins only .
- Structural residue position.

lobes is inaccessible even to water molecules from below, an isolation particularly significant for the reactive site region (5,6) shown shaded in the projected view.

Polypeptide Backbone. The barreling curve of the β structure is complex; individual strands both turn and twist. Fig. 5 shows the molecular hydrogen bonding pattern; the three β bends in the β sheet are, respectively, A7+B10 type I (7), C31+D34 (K38) type III (i.e., 3₁₀ helix) and rim segment 47(K53)+E50 (K57) type II. There is a "wide" β bulge (8) in the left-hand edge of the sheet which involves Proll and Gln12 in strand B and Gln6 in the opposite A strand. The general preference for Pro in the first position has been

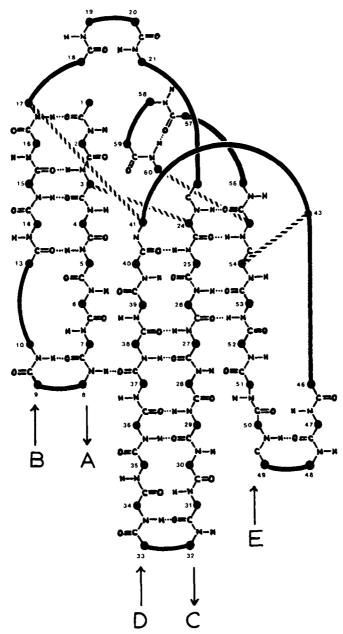


Fig. 5. Hydrogen bonding pattern of erabutoxin b polypeptide chain. The C=O and H-N groups are joined by dotted lines when the O-N distance \leqslant 3.7 Å. Disulfide bridges are shown with striped lines.

noted earlier (8). Strands B and C are joined through the tapered neck region by a "plain +3 connection" which includes a type I β bend 18-21; strands D and E are joined by a right-handed $2_{\rm X}$ cross-over connection (9). The E strand leads into a type I β bend, 57-60 (K64-K68) in the C-terminal closed ring.

The dihedral angles about ~S-S of the four disulfide bridges which maintain the β structure, all lie close to 90°. Three linkages are right-handed; that joining Cysl7 and Cys41 (K45) is left-handed. The disulfide bridge 43-54 (K49-K61) is Gauche.Gauche.Trans; the other three are Gauche.Gauche. Gauche. These findings agree with the conclusion of the laser Raman solution studies of erabutoxin b (10).

Homologous Side Chain Distribution. The overall sequence homologies of invariant and conservatively substituted positions are further extended in the short series toxins by 6 more invariants and 2 more conservative substitutions. In a broad sense the extent and distribution of all common invariant or type-conserved residues define the principal features of the erabutoxin b structure as short series prototype and long series model. Most of these residues are found within the reactive site (1,2,5,6) region 32-49...32 (K33-K56...K33) formed by the two right-hand lobes of the molecule and shown shaded in Fig. 4. In the AB loop of the short-series toxins, the limited number of common residues may imply minor conformational variations; in the tapered neck region the one or two residue deletions found in positions 18,19, or 20 demand conformational variations.

There are residues which evidently play a key structural role; they lie within or are bound to the reactive site and are shown enclosed in open hexagons in Fig. 4. These include four invariant glycines, two in the β bends and two (one a short series invariant) at positions of close approach of two chains. Pro44 (K50) stabilizes the rim segment turn. Two further residues, the type-conserved position Glu21 (Glu/Asp) and the invariant Asn61 (K69) form hydrogen bonds to atoms in neighboring segments of the main chain.

A second group of residues has been designated "functional" because of probable involvement in receptor binding (5,6). With one exception, all point up along $C\alpha$ - $C\beta$ into the sweeping hollow of the reactive site. The exception Val46 (K52) forms part of the banked wall of this concavity. The functional residues have been sorted into reactive groupings (5,6). Toxicity is less than normal when some functional residues are chemically modified or are found replaced in certain naturally occurring deviant toxins. Other hydrophobic residues have been designated "functional" on the basis of indirect evidence. We will consider the structure-function relationships and the effect of our recent findings on the details of the earlier model elseshere.

The designations "structural" and "functional" are in some instances too restrictive; the two roles are not necessarily mutually exclusive. In a reactive grouping, one or more "functional" residues may position the residue which binds directly to receptor. Equally, some "structural" residues may be required for proper local functional expression, as for example, Gly34 (K38) in the acetylcholine mimetic association and binding of Asp31 and Arg33 (K37) proposed earlier (2,5,6,11).

It is a remarkable feature of the neurotoxin homology that functional residue distribution defines, and β structure stereochemistry demands a sequence distribution which involves an interrupted and frequently alternating series of invariant and/or conservative substitutions rather than a continuous segment of identical or near-identical sequence.

The atomic coordinates on which these conclusions are based may be expected to shift somewhat after refinement. Model studies have shown that differences between the long and short series toxins do not need to affect significantly the principal structural features we have described here (5,6).

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