

BIOCHEMICAL JOURNAL LETTERS

A standard numbering scheme for the Class A β -lactamases

β -Lactamases catalyse the hydrolysis of the β -lactam ring of penicillins, cephalosporins and related compounds, and thereby protect the bacteria which elaborate the enzymes against the action of these antibiotics. A recent review of the molecular properties of the proteins is given by Coulson (1985).

The proteins have been classified on the basis of their sequences; the largest group is called 'Class A' (Ambler, 1980). Enzymes of this class are found in Gram-negative and Gram-positive organisms, cell-bound, periplasmic or secreted, and derived from plasmid or chromosomal genes. For a recent survey of this and the other sequence classes, and of the relation of β -lactamases to other proteins such as the cell-wall synthesis enzymes, see Joris *et al.* (1988). Mechanistic and structural studies (including X-ray crystallography) are in progress with at least half-a-dozen of the Class A enzymes. There is no doubt that the proteins are homologous, and it is to be expected that molecular studies of any of the Class A enzymes can be extended to other members of the class. However, the known sequences vary considerably in length. The leader peptides are not in general homologous, and have a wide range of lengths. Some sequences are known only from the protein (lacking the leader sequence), and some proteins show different processing for the cell-bound and secreted forms, etc. In addition, it is clear that there are differences in length internal to the processed forms of the proteins, and these are presumably associated with surface loops of different lengths connecting conserved internal structures.

For these reasons, homologous residues from different Class A sequences generally differ in their 'natural' or 'sequential' numbers. In order to avoid the confusion and inconvenience that arises in the comparison of molecular studies of different Class A enzymes, we propose here a standard numbering scheme for this group of proteins. The scheme (Fig. 1) has been generated by aligning 20 Class A sequences, and attaching numbers to the alignment in order to preserve as much as possible of the numbering used by Ambler (1980) for the first four members of the class.

It is not intended that the present schemes will replace the natural or sequential scheme for individual proteins. The scheme will be used in the context of comparison of homologous residues, and the standard numbers will be indicated by the label 'ABL' (for Class A β lactamase). Thus 'Val-77 (ABL80)' of the R-TEM enzyme will indicate a residue homologous to Leu-75 of PSE-4, with the same ABL number.

Alignment of protein sequences is most reliable when it is based on X-ray crystal structures of all the proteins concerned, and it cannot be ruled out that X-ray crystallography will suggest changes in the detail of the alignment in Fig. 1. However, there is no doubt the alignment is mostly correct. Fragments of sequence have been omitted in several places (particularly with

the more recently added sequences) where homology is uncertain. It is a virtue of the scheme we propose that future corrections and adjustments to individual residues will not alter the overall numbering and no changes will be made to accommodate new, longer sequences. Nor should the alignment of Fig. 1 be regarded as a definitive statement of the homology relations which exist amongst these proteins. For example, any worker who does not regard the DI (ABL 116–117) of the *Staphylococcus aureus* protein as equivalent to the GM sequence which is generally found here will simply not use the ABL numbers to refer to the *S. aureus* residues.

In order to give the active site serine residue the ABL number 70, it was necessary to start the numbering within some of the leader sequences. Expressed sequences start about ABL31, and though an alignment is shown for earlier residues, numbers 1–30 are unlikely to be used in practice since the leader sequences are not homologous.

A network of sequence relations has been recognized amongst many of the proteins which interact with β -lactams. It is possible, especially as X-ray crystal structures become available, that the current scheme can be extended to, for example, the Class C proteins.

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	1		50		100					
<i>Klebsiella pneumoniae</i>	MRYVRL	CVISLLATLP	LVVYAGPQPL	EQIKQSESQ	SGRVGMVEMD	LANGRTLAAV	RADERFPMVS	TFKVLKCGAV	LARVDAGLEQ	LDRRIHYRQQ
PIT-2			SPQPL	EQIKLSESQ	SGRVGMIEHD	LASGRITLAV	RADERFPMMS	TFKVLKCGAV	LARVDAGDEQ	LERKIHYYRQ
R-TEM	MSIQHFRV	ALIPFFAAFC	LPVFAHPTL	VYKVDQEEL	GARYGVIELD	LNSGKILES	RPERFPMMS	TFKVLKCGAV	LSRVADAGQE	LGRRIHYSQN
<i>Pseudomonas aeruginosa</i>	CHFLSVPAI	LGCVGLICTS	AYAMDTGIL	LAVTQEETL	GARYGVAID	TDSQLTW.QH	RPERFPLNS	THKAFSCAAV	LAQADRHLKN	LEGAIPERT
PSE-4	GVTYMKFLA	FSLLIPSVVF	ASSSKFQVVE	QDVKAIEVSL	SARIGVSVLD	TQNGEYV.DY	NGNQRFPLTS	TFKTIACAKL	LYDAEQGVKN	PVNSTVEIKKA
<i>Rhodopseudomonas capsulata</i>	TVLSRVATGL	ALGLSMATAS	LAGTPVEALLS	ETVARIEEQL	GARYGLSLME	TGTGWSV.SH	REDELFLMS	TKVQVPCGAI	LARWDAGRLS	LSDALPVYKA
<i>Actinomadura R39</i>		AEPA	SAEVTAEDLS	GEFERLESF	DARLGVYAVD	TGTGEEV.FH	RADERFPGYAS	THKAFALAVL	LGQ..NTPEE	LEEVITYTEE
<i>Bacillus cereus</i> 569H	TSLEAFTGES	LQVEAKEKGTG	QVQKHKNQATH	KEFSQLEKFF	DARLGVYAVD	TGTNQT.I.SY	RPNERFAFAS	TYKALAAGVL	LQQ..NSTK	LDEVITYTKE
<i>Bacillus cereus</i> 5/B	TSLVFTTGGG	LQVEAKEKGTG	QVQKHKNQATH	KEFSQLEKFF	DARLGVYAVD	TGTNQT.I.SY	RPNERFAFAS	TYKALAAGVL	LQQ..NSTK	LDEVITYTKE
<i>Bacillus cereus</i> III	LIGCSNSNTQ	SESNKQTNQT	NQVQKQENKRN	HAFAKLEKEY	NAKLGIVYALD	TSTNQT.V.AY	HADDRFAFAS	TSKSLAVGAL	LRQ..NSIEA	LDERITYYTRK
<i>Bacillus licheniformis</i>	LFSCVALAGC	ANNGTNASQP	AEKNEKTEMK	DDFAKLEEQF	DAKLGIFALD	TGTNRTV.AY	RPDERFAFAS	TIKALTGVGL	LQQ..KSIED	LNQRITYYTR
<i>Streptomyces badius</i>	..SDSTAPPS	SAKPATSASA	SLP.RPKPYT	GDFKLEREF	DARLGVYAVD	TGTGREV.TH	NDRARFAFAS	TYKALAAGVL	LS	SLDG
<i>Streptomyces cacaoi</i> blaU	ESSADAPEA	GSAPSSSAAA	HKPGVEPEYA	AELKALEDEF	DVRLGVYAVD	TGSGREV.AY	RDGERFPYNS	TFKALCGAV	L	DRVVKYSD
<i>Streptomyces cacaoi</i> ULG	ACGQASGSES	GQQPGLGGAD	EAHVSADAEH	KEFRALKEFF	DAHPPVYAVD	TRDQGEI.TH	RADERFAFAS	TYKALAAGVL	LAQV	DKVVHYGQD
<i>Klebsiella oxytoca</i>	MAA	AAVPLLLASG	SLWASADAIQ	QKLDLEKRS	GGRLGVALIN	TA QTL Y	RGDERFAMCS	TGKVMAAAV	LKQ	VNKRLEIKKS
<i>Staphylococcus aureus</i>	MKKL	IFLIVIALVL	SACNSNSSHA	KLNDLEKCY	NAHGIVYALD	TKSGKEV.KF	NSDKRFAYAS	TSKALNSAIL	LEQV..PYNK	LNKRVHINKD
<i>Streptomyces aureofaciens</i>	TMAALLPAGG	AAAYASTAK	APAAEADLSG.	..LRALREKQY	DAHPPVYAVD	TGTGREV.TH	RAGERFPYNS	TFKALAAGVL	LQVDA	LTKRIHY
<i>Streptomyces albus</i>	ALAAATLVPG	TAAHSSGGRG	HGSGSVSDAE	RRLAGLERAS	GARLGVYAVD	TGSGRTV.AY	RADELFPMS	VFKLSSAAV	LRD	LDR D
<i>Streptomyces lavendulae</i>	AVAGPLPGGS	TAF.A.....	..APRGNPDVE	QRLRALEQY	SARLGVYAVD	TATGRTV.LH	RAEERFPMS	VFKTLAAVAV	LR	LDR
<i>Streptomyces fradiae</i>	ALAATAAAG	PAHA.....	..APRGNPDVE	RRLRALEQY	SARLGVYAVD	TATGRTV.AY	RADERFPMS	VFKTLAAVAV	LR	LDR
Consensus	.saa.aa.g.	aavpslaaag	.apgsnpa..	ke.kalEkqf	darlGvya.d	tgtgrtv.ay	raderfPms	tFkAla..av	L.q.....e	L..ritytk.
	101		150		200					
<i>Klebsiella pneumoniae</i>	DLVDYSPVSE	KHLVDGMTIG	ELCAAAITLS	DNSAGNLLLA	TVGGPAGLTA	FLRQIGDNVT	RLDRWETALN	EALPGDARD	TPASMAATL	RKLLTAQHLS
PIT-2	DLVDYSPVSE	KHLADGMTVG	ELCAAAITMS	DNSAANLLLT	AVGGPAGLTA	FLRQIGDNVT	RLDRWETELN	EALPGDARD	TPASMAATL	RKLLTSQRLS
R-TEM	DLVEYSPVTE	KHLTDGMTVR	ELCSAAITMS	DNTAANLLLT	TIGGPKELTA	FLRQIGDNVT	RLDRWEPENL	EAIIPNDEROT	TMPAAATL	RKLLTGLL
<i>Pseudomonas aeruginosa</i>	ALVTVSPVTE	LTLR	ELCRAAVSIS	DNTAANLLD	AIGGARTFTA	FMRISGDDKT	RLDRPEPELN	EATPGDARD	TPPIAARSL	QTLLLDGLVS
PSE-4	DLVTVSPVIE	KQVQAATLD	DACFAHTTS	DNTAANILIS	AVGGPKGVTD	FLRQIGDKET	RLDRIEPELN	EAGLGLRDT	TPKALJLSTL	NKFLFGSALS
<i>Rhodopseudomonas capsulata</i>	DLVVPYAPVTE	MTLD	ELCLAAIDMS	DNVAANILIG	HLGGPEAVTQ	FFRSVGDPTS	RLDRIEPELN	DFASGDEROT	TSPAAMSETL	RALLLDGLVS
<i>Actinomadura R39</i>	DLVDYSPITE	QHVDTGMTLL	EVADAAVRHS	DNTAANLLFE	ELGGPEGFE	DMRELGDVVI	SADRIEPELN	EVPPGETROT	STPRAMAGSL	EAFVLGDVLE
<i>Bacillus cereus</i> 569H	DLVDYSPVTE	KHVDGTMLKLG	EIAEAAVRS	DNTAGNIFL	KIGGPKGYEK	ALRHMGRDRT	HSNRFETELN	EAIPIGDRDT	STAKAIATNL	KAFTVGNALP
<i>Bacillus cereus</i> 5/B	DLVDYSPVTE	KHVDGTMLG	EIAEAAVRS	DNTAGNIFL	KIGGPKGYEK	ALRHMGRDRT	HSNRFETELN	EAIPIGDRDT	STAKAIATNL	KAFTVGNALP
<i>Bacillus cereus</i> III	DLVSNYPITE	KHVDGTMLK	ELADASLRS	DNAQNLILK	QIGGPESLKK	ELRKGIDEV	NPERFEPELN	EVNPGETQDT	STARALVTL	RAFALEDKLP
<i>Bacillus licheniformis</i>	DLVSNYPITE	KHVDGTMLK	ELADASLRS	DNAQNLILK	QIGGPESLKK	ELRKGIDEV	NPERFEPELN	EVNPGETQDT	STARALVTL	RAFALEDKLP
<i>Streptomyces badius</i>	DLVAHSPVTE	KHVDGTMLK	ELCDASVRS	DNTAANLLFD	GPKGLDA	SLEKLGDDIT	RMDREPELS	RWVPGKERDT	STPRALAE	RAFVLGKALR
<i>Streptomyces cacaoi</i> blaU	DLVDNSPVTE	KHVEDGMTL	ALCDAAVRS	DNTAANLLFE	TVGGPKGLDK	TLEGLGDHVT	RHERVEPELS	RWEPGSKRDT	STPRAFKDL	RAYVLGDVLA
<i>Streptomyces cacaoi</i> ULG	AILPNSPVTE	KHVDGMTL	ELCDAAVRS	DNTAANLLFD	QVGGPKGLDK	VKQKLGDDHT	SMDRYEQLG	SAVPGDPRDT	STPRAFA	
<i>Klebsiella oxytoca</i>	DLVWVSPITE	KHLQSGHTLA	ESLAAALQYS	DNTAMNKHS	F	GDVTF	RLDRTEPELN	SAIPGDKRDT	TPPLAMAESL	RKLLTGLNALG
<i>Staphylococcus aureus</i>	DIVAVSPILE	KYVGDITLK	ALIEASHTYS	DNTAMNKIK	EIGGKIKVKQ	RLKELGDKVT	NPVRYEIELN	YSPSKSKD	STPAAFGKTL	NKLIANGKLS
<i>Streptomyces aureofaciens</i>		PVT	GMTGA	ELCAAAVSES	DNGAGNLLLR	ELDGPITGR	FLRQIGDIT	RLDRWEPALN	SAEPRVDT	TPSGAIGRTF
<i>Streptomyces albus</i>	DV	APETG K	GHTVE	ELCEVSTIS	DNCAANLHR	FLRQIGDRT	RLDRWEPALN	SAEPVDT	TPSPRAITRTY	GRVLGDALN
<i>Streptomyces lavendulae</i>		FGPVT	GHTVE	RLCAAAICQS	DNAANLLLR	ELGGPEAVTR	FLRQIGDRT	RLDRWEPALN	SAEPGLTDT	TPSPRAIGRTY
<i>Streptomyces fradiae</i>		YSPV	GHTVA	ELCEATLRS	DNTAANLLLR	DLGGPTAVTR	FLRQIGDRT	RLDRWEPALN	SAEPGLTDT	TPSPRAIGRTY
Consensus	dlvdyspvte	khvdtgmtl	elcdaavrs	DntAanllr	elggpkgvta	flrsldg.vt	rldrWepeln	eaepgdkrdt	tpspriaertl	r.llldgals
	201		250		295					
<i>Klebsiella pneumoniae</i>	ARSQQQLLQW	MVDDRAGPL	IRAVLPPGF	IADKTGAG.E	RGARGIVALL	GP.DGKPERI	VVIYLRDTPA	SMAERNQHA	GIGQR	
PIT-2	ARSQRLLQW	MVDDRAGPL	IRSVLPAGVF	IADKTGAG.E	RGARGIVALL	GP.NNKAERI	VVIYLRDTPA	SMAERNQHA	GIGAAALIEHW	QR
R-TEM	LASRQQLD	MEADKAVAGL	LRSLPAGVF	IADKSGAG.E	RGSRGIIAAL	GP.DGKPSRI	VVIYTTGSAQ	TMDERNRQIA	EIGASLIKHW	
<i>Pseudomonas aeruginosa</i>	APARNELTGW	HLGDDQVADL	LRAGLPADW	IADKSGAG.G	HGSRGIIAVV	WP.PKRSAVI	VVIYITQATA	SMSANSQAVS	RIGSALAKAL	Q
PSE-4	EMNQKLGES	MVNNQVTGNL	LRSLPAGW	IADRSAGG.G	FGARSITAVV	WS.EHQAPII	VSIYLAQTGA	SMEERNDIV	KIGHSIDFVY	TSQSR
<i>Rhodopseudomonas capsulata</i>	PEARQKLAEW	MRHGGVTGAL	LRAEAEADWL	ILDKSGGG.S	H.TRNLVAVI	QP.EGGAPWI	ATMFIISDTA	EFVEFNEALK	DLGRAVVAV	RE
<i>Actinomadura R39</i>	EGPRDVLTE	LLNNTTGDDEL	IRAGVPEDWR	VGDKTGTTG.S	HGSRNDIAVV	WP.PEDDPIV	IADVSTREGE	DAEFDNDLIA	GATEVVEAL	AP
<i>Bacillus cereus</i> 569H	AEKRIKILTEW	MKGNATGDGL	IRAGIPTDWW	VGDKSGAG.S	YGRNDIAVV	WP.PNRAPII	IAILSSKDEK	EAIYDNQLIA	EATKIVKAL	R
<i>Bacillus cereus</i> 5/B	HQKRNILTEW	MKGNATGDGL	IRAGVPTDWW	DADKSGAG.S	YGRNDIAVV	WP.PNRSPII	IAILSSKDEK	EAEYDNQLIA	EAEVVIDAI	K
<i>Bacillus cereus</i> III	SEKRELLVDW	MKRNITGDGL	IRAGVPGKWE	VADKTGAG.S	YGRNDIAII	WP.PNKCPIV	LSILSNHDEK	DAEYDNLIA	DATKIVLETL	KVTNK
<i>Bacillus licheniformis</i>	SEKRELLD	MKRNITGDAL	IRAGVPGWE	VADKTGAA.S	YGRNDIAII	WP.PKGPVIV	LAVLSSRDKK	DAKYDNLIA	EATKIVKAL	NMNGK
<i>Streptomyces badius</i>	APERAGLTTW	LRTNTTGDVAV	IRAGVPEDWR	VGDKTGTTG.S	YGARNDIAVV	WP.PDSAPIV	IAILSHRGTG	DAEPDNLIA	EASVVDVSL	SS
<i>Streptomyces cacaoi</i> blaU	EGDRKQLTTW	LRNNTTGDGL	IRAGVROGVV	VGDKTGTTG.S	YGARNDIAVV	WR.PDGRPLV	LVNVMHGHGK	DAEDELIA	RATEVVDRL	G
<i>Streptomyces cacaoi</i> ULG	RLQLNDW	MSGKPTGDAL	IRAGVPKDVK	VEDKSGQV.K	YGRNDIAVV	RP.PGRAPIV	VSVHSHGDTQ	DAEPHSELIA	EAGLVADGL	K
<i>Klebsiella oxytoca</i>	EQQRQLLVTW	LKGNNTTGGQS	IRAGLPASWA	VGDTKGAG.D	VGDTTNDIAVI	WP.ENHAPLV	LVTYFTGQQQ	DAEKSRKEVLA	AAAKIVTEGL	
<i>Staphylococcus aureus</i>	KENKFLLDL	MLNKNKSGDTL	IKDGVPKDYK	VADKSGQAT	YGVANDVAVFV	YPKGQSEPIV	LVIFTKNDK	SKPNDKLIS	ETAKSVMEK	
<i>Streptomyces aureofaciens</i>	AGDRKRLTGW	LVANTTNRPT	FRAGLPDDTW	LADKTKGQET	YGVANDVGVV	QP.PGRAPLV	LSVLSTKFPD	DKPTNDPLIA	KAALVAGEL	T
<i>Streptomyces albus</i>	PRDRRLTSW	LLANTTSGDR	FRAGLPDDTW	LGDKTGAG.R	YGTNNDAGVT	WP.PGRAPIV	LTVLTAKEFQ	DAARDNLVA	DAARVLAETL	G
<i>Streptomyces lavendulae</i>	PRDRRLTGW	LLANTTSTER	FRKGLPADWT	LGDKTGGG.A	YGTNNDAGVT	WP.PHRPPV	MVVLTHDRP	DAEADNLVA	KTAALLASAL	G
<i>Streptomyces fradiae</i>	AHDRERLTRW	MLDNRTSDER	FRKGLPADWT	LADKTKGGA.D	YGTNNDAGVA	WP.PGRPPV	LAQVTRTFP	DAEADNLVA	EAARLEAEM	TD
Consensus	ae.rkQLtdw	mlgnttgdal	iraglpadvw	vadktgag.s	ygrndiavv	wp.pgrapiv	lailstkd..	dae.dn.lia	eaakvvaal	.s.k

Fig. 1. Alignment of 20 Class A β -lactamases numbered according to the ABL scheme

The sequences are referred to by their most familiar names. '.' indicates a postulated deletion; blank spaces indicate one or more residues omitted from the alignment. Leader sequences before position 1 are omitted. Note that single tyrosine residues have been omitted from the *Streptomyces badius* and *Streptomyces cacaoi* sequences at position 241. Publication references are as follows: *Klebsiella pneumoniae*: Arakawa, Y., Ohta, M., Kido, N., Fujii, Y., Komatsu, T. & Kato, N. (1986) FEBS Lett. **207**, 69-74; PIT-2: Barthelemy, M., Peduzzi, J. & Labia, R. (1988) Biochem. J. **251**, 73-79; R-TEM: Sutcliffe, J. G. (1978) Proc. Natl. Acad. Sci. U.S.A. **75**, 3737-3741; *Pseudomonas aeruginosa* and *Rhodopseudomonas capsulata*: Campbell, J. I. A., Scallan, S. A., Gibson, T. & Ambler, R. P. (1989) Biochem. J. **260**, 803-812; PSE-4: Boissinot, M. & Levesque, R. C. (1990) J. Biol. Chem. **265**, 1225-1230; *Actinomadura R39*: Houbba, S., Molitor, C., Willem, S., Ghuyens, J.-M., Frère, J.-M., Duez, C. & Dusart, J. (1989) FEMS Microbiol. Lett. **65**, 241-246; *Bacillus cereus* 569H and 5/B: Madgwick, P. J. & Waley, S. G. (1987) Biochem. J. **248**, 657-662 and Madonna, M. J., Zhu, Y. F. & Lampen, J. O. (1987) Nucleic Acids Res. **15**, 1877; *Bacillus cereus* III: Husain, M., Pastor, F. I. J. & Lampen, J. O. (1987) J. Bacteriol. **169**, 579-586; *Bacillus licheniformis*: Neugebauer, K., Sprengel, R. & Schaller, H. (1981) Nucleic Acids Res. **9**, 2577-2588; *Streptomyces badius*, *cacaoi* blaU, *lavendulae* and *fradiae*: Forsman, M., Haggstrom, B., Lindgren, L. & Jaurin, B. (1990) J. Gen. Microbiol. **136**, 589-598; *Streptomyces cacaoi* ULG: Lenzi, M. V., Ishihara, H., Dusart, J., Ogawara, H., Joris, B., Van Beumen, J., Frère, J.-M. & Ghuyens, J.-M. (1988) FEMS Microbiol. Lett. **49**, 371-376; *Klebsiella oxytoca*: Arakawa, Y., Ohta, M., Kido, N., Mori, M., Ito, H., Komatsu, T., Fujii, Y. & Kato, N. (1989) Antimicrob. Agents Chemother. **33**, 63-70; *Staphylococcus aureus*: Ambler, R. P. (1975) Biochem. J. **151**, 197-218 and McLaughlin, J. R., Murray, C. J. & Rabinowitz, J. C. (1981) J. Biol. Chem. **256**, 11273-11282; *Streptomyces aureofaciens*: G. Tiraby, unpublished work; *Streptomyces albus*: G. Dehottay, P., Dusart, J., De Meester, F., Joris, B., Van Beumen, J., Erpicum, T., Frère, J.-M. & Ghuyens, J.-M. (1987) Eur. J. Biochem. **166**, 345.