Bridging β-Lactam Coordination at Dinuclear Zinc Sites

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Dedicated to Professor Heinrich Vahrenkamp on the occasion of his 65th birthday

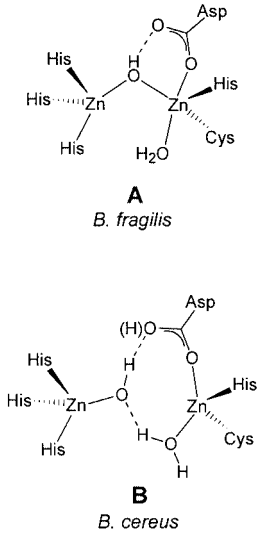
Keywords: Dinuclear complexes / Metalloenzymes / N ligands / Pyrazolate ligands / Zinc

Two highly preorganized dizinc scaffolds based on compartmental pyrazolate ligands are found to incorporate 2-azetidinone in its deprotonated β-lactamide form as an N,O-bridging ligand within the dimetallic pocket. Both dizinc β-lactamide complexes **3**·$(ClO_4)_2$ and **4**·$(ClO_4)_2$ have been characterized structurally and spectroscopically, revealing a strengthening of the β-lactamide C–N bond and a weakening of the C=O bond relative to free 2-azetidinone. These findings contrast the reverse geometrical changes observed recently by Brombacher and Vahrenkamp for β-lactamide *N*-bound to only a single zinc ion, thus underlining the particular dimetallic effect that is achieved by the cooperativity of two adjacent metal ions.

Introduction

β-Lactamases are a class of enzymes that efficiently catalyze the hydrolytic opening of β-lactam rings.[1,2] Since the β-lactam motif is a crucial subunit of the largest group of therapeutically useful antibiotics comprising the penicillin, cephalosporin, and carbapenem families, bacteria express β-lactamases in order to escape the action of those important drugs. Nowadays, increasing resistance against β-lactam antibiotics poses a serious clinical problem.[3–5] Unfortunately, most clinically useful inhibitors are inactive towards a particular class of β-lactamases, which depend on one or two zinc(II) ions within their active site.[6–8] These so-called metallo-β-lactamases hydrolyze a wide range of substrates, and insight into the binding and transformation of β-lactam compounds by such zinc active sites is considered not only of fundamental interest, but may also contribute to the development of efficient mechanism-based inhibitors.

Detailed information about the active-site structure of several metallo-β-lactamases has been gained from X-ray crystallography and other methods, in particular for the enzymes from *Bacillus cereus* and *Bacteroides fragilis*.[8,9] The majority of these sites have similar unsymmetrical dizinc binding motifs and a shared water/hydroxide ligand in a typical bridging position (**A**),[10–15] but structural evidence has also been reported for a nonbridged form with a loose ligand arrangement and a larger Zn···Zn distance of 4.4 Å.[14] The latter configuration has been reproduced in theoretical models by an O_2H_3 unit between the two zinc ions (**B**; Scheme 1),[16] and such an O_2H_3 moiety has indeed been proposed as a possible functional motif in oligozinc hydrolases.[17–19]



Scheme 1.

Although the dizinc form of the metallo-β-lactamases from *B. fragilis* and *B. cereus* is usually considered as the biologically active form, the role of the second Zn^{2+} re-

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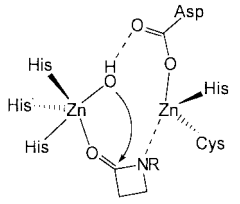
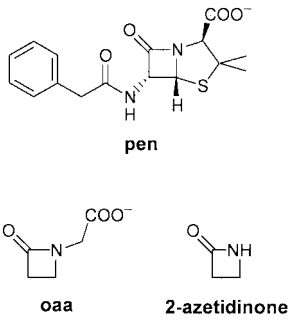
mains controversial,[20,21] and distinct mechanisms may be relevant for the mono- and dimetallic forms.[9,21–23] Details of the catalysis by dizinc metallo-β-lactamases are still a subject of debate, although it is generally postulated that interaction of the β-lactam carbonyl group with a zinc ion polarizes the C–O bond and allows nucleophilic attack by a metal-bound hydroxide ion with fission of the C–N bond. Subsequent protonation of the β-lactam N atom and dissociation of the acyl group would liberate the ring-opened product (Scheme 2).[22] A ring-opened form of the substrate has been detected as an intermediate in the hydrolysis of nitrocefin by the *B. fragilis* enzyme;[24] its identity as a zinc(II)-bound *N*-deprotonated species formed by C–N bond cleavage was corroborated by model studies.[25]



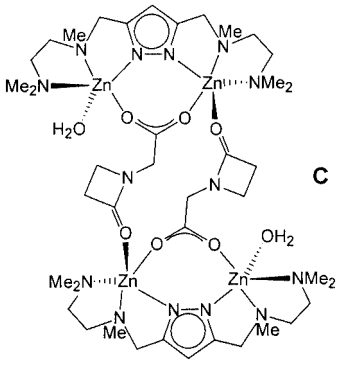
Scheme 2. Proposed β-lactam cleavage step of dizinc metallo-β-lactamase.

The pH profiles of the *B. cereus* reaction indicate that the second zinc(II) center is not required for nucleophile activation, but its role in orienting the attacking nucleophile and in stabilizing reaction intermediates has been proposed.[22,26–28] While several groups have dealt with the hydrolysis or methanolysis of β-lactams by simple transition-metal salts, including Zn^{2+} salts,[29,30] very few studies have employed preorganized dinuclear zinc(II) complexes as functional mimics of metallo-β-lactamases.[25,31–33] Such models might provide valuable insights into, inter alia, the mechanistic role of the second Zn^{2+} ion, cooperative effects of the adjacent metal ions, and possible binding modes of the substrate. Lippard et al. recently reported an in-depth study of nitrocefin hydrolysis mediated by some phenol- and naphthyridine-based dizinc complexes.[31,32] Preferential metal ion coordination of typical β-lactam substrates through a monodentate carboxylate group was inferred from ^{13}C NMR and IR spectroscopy.[31,32]

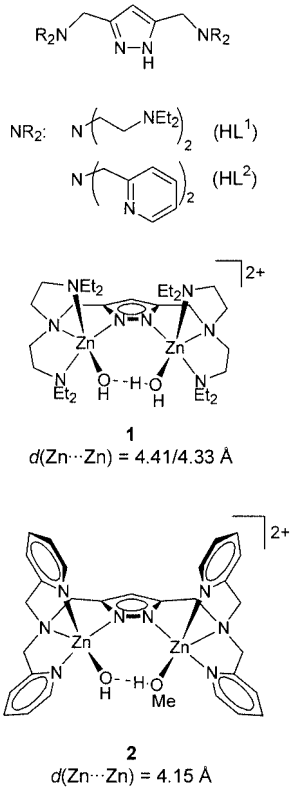
Structure–activity correlations have been deduced for the hydrolytic cleavage of penicillin G (pen; Scheme 3) mediated by a series of pyrazolate-based dizinc(II) complexes with tunable Zn···Zn distances.[33] The drastic differences in activity for the various systems were explained on the basis of the necessity of suitably oriented, accessible coordination sites that are required to bind and activate both the nucleophile and the substrate. The molecular structures of several adducts of such pyrazolate-based dizinc scaffolds with the small substrate analog oxazetidinyl acetate (oaa) confirmed that binding of the zinc ion to the carboxylate group is favored over binding to the β-lactam amide group. However, additional zinc coordination by the β-lactam amide O atom may still be induced under suitable circumstances, and was observed crystallographically for the first time in the tetranuclear complex **C** (Scheme 4), which reveals significant



Scheme 3. β-Lactams used in this and previous work with dizinc complexes **1** and **2**.



Scheme 4. Complex **C** featuring β-lactam amide-O coordination of oaa.[33]



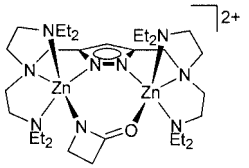
Scheme 5. Ligands and complexes used in this work.

changes of the internal geometry of the β-lactam moiety that are likely to facilitate subsequent hydrolytic ring cleavage.[33]

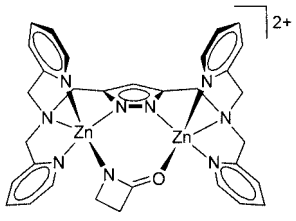
In this contribution we report the synthesis and crystallographic characterization of adducts between the most simple β-lactam, 2-azetidinone, and two highly preorganized dizinc complexes **1** and **2** (Scheme 5)[34,35] that mimic the loosely bridged type **B** form (Scheme 1) of the active site of the *B. cereus* β-lactamase.

Results and Discussion

Complexes **1** and **2** were prepared in situ from the respective ligand HL, 2 equiv. of base (KO*t*Bu), and 2 equiv. of $Zn(ClO_4)_2 \cdot 6H_2O$; 1 equiv. of 2-azetidinone was then added to the reaction mixture, and colorless single crystals of **3**·$(ClO_4)_2$·MeOH and **4**·$(ClO_4)_2$·acetone could be obtained upon recrystallization of the resulting complexes from methanol or acetone solutions, respectively (Scheme 6). The FAB mass spectra of solid samples show prominent peaks at *m*/*z* = 818 (**3**) and 786 (**4**) with an isotopic distribution pattern characteristic for the ions $[L^1Zn_2(C_3H_4NO)(ClO_4)]^+$ and $[L^2Zn_2(C_3H_4NO)(ClO_4)]^+$, respectively, suggesting the formation of 1:1 adducts between the dizinc complexes and deprotonated 2-azetidinone. The IR spectrum of **3**·$(ClO_4)_2$ reveals a strong absorption at 1606 cm^{-1} for the β-lactam $\nu(C{=}O_{amide})$ stretch, which is significantly shifted to lower frequency compared to free 2-azetidinone (IR: $\tilde{\nu}$ = 1723 cm^{-1}; Raman: $\tilde{\nu}$ = 1697 cm^{-1}).[36,37] This shift indicates Zn coordination by the lactam O atom. In the case of **4**·$(ClO_4)_2$, the $\nu(C{=}O_{amide})$ vibration cannot be identified unambiguously, since several strong bands of the pyridyl groups also appear in that region (1629, 1606, 1589, 1565 cm^{-1}). The molecular structures of **3** and **4** were elucidated by X-ray crystallography and are depicted in Figures 1 and 2, respectively.



3
d(Zn···Zn) = 4.28 Å



4
d(Zn···Zn) = 4.02 Å

Scheme 6. Complexes **3** and **4** prepared in this work.

In both cases the $\{LZn_2\}$ entities of the starting complexes **1** and **2** are fully conserved. The 2-azetidonone is

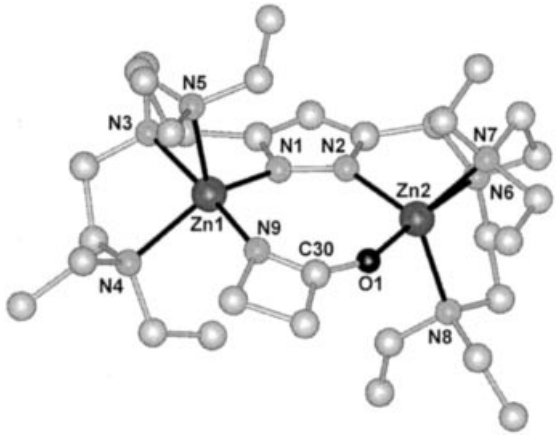


Figure 1. View of the molecular structure of **3**. In the interests of clarity, all protons have been omitted. Selected interatomic distances [Å] and angles [°]: Zn1–N1 2.051(3), Zn1–N3 2.294(4), Zn1–N4 2.187(4), Zn1–N5 2.164(4), Zn1–N9 2.032(4), Zn2–N2 2.009(4), Zn2–N6 2.238(4), Zn2–N7 2.161(5), Zn2–N8 2.155(5), Zn2–O1 1.958(4), C30–O1 1.239(7), C30–N9 1.292(7); N9–C30–O1 131.5(5).

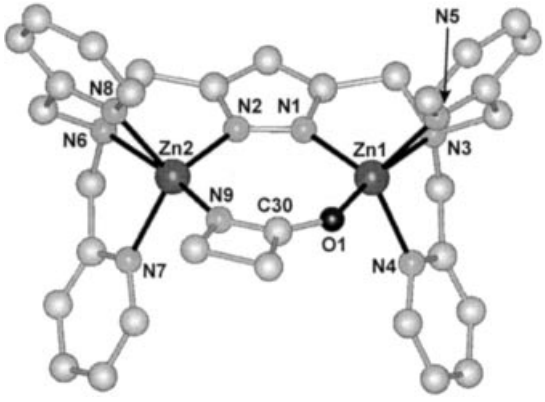
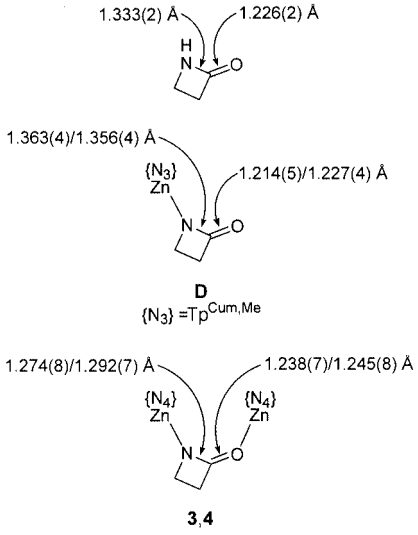


Figure 2. View of the molecular structure of **4**. In the interests of clarity, all protons have been omitted. Selected interatomic distances [Å] and angles [°]: Zn1–N1 1.984(4), Zn1–N3 2.281(5), Zn1–N4 2.062(5), Zn1–N5 2.056(5), Zn1–O1 1.973(4), Zn2–N2 1.993(5), Zn2–N6 2.303(5), Zn2–N7 2.074(5), Zn2–N8 2.081(5), Zn2–N9 1.980(6), C30–O1 1.245(8), C30–N9 1.274(8); N9–C30–O1 130.9(6).

incorporated in its *N*-deprotonated lactamide form within the dimetallic pocket and bridges the two zinc ions in an N,O-fashion at a Zn···Zn distance of 4.277(1) Å (**3**) and 4.015(1) Å (**4**). A similar Zn···Zn distance of 4.180 Å was observed in a carbonato-bridged complex of a related pyrazolate ligand.[18] All zinc ions in **3** and **4** are found in a slightly distorted trigonal-bipyramidal coordination environment (**3**: τ = 0.88 for Zn1 and 0.94 for Zn2; **4**: τ = 0.90 for Zn1 and 0.87 for Zn2).[38] The bond lengths between the zinc ions and the N-donor atoms of the dinucleating ligand scaffolds L are in the normal range, with bonds between Zn and the pyrazolate N atom being the shortest [1.984(4)–2.051(3) Å] and bonds between Zn and the backbone N3/N6 atoms being the longest [2.238(4)–2.303(5) Å]. In the latter case, the Zn–N bonds *trans* to the lactamide N

atom are somewhat longer than those *trans* to the lactamide O atom.

The most interesting metric parameters are those of the bound β-lactamide, which can be compared to those of free 2-azetidinone[39] and to the β-lactamide subunit of a $Tp^{Cum,Me}$Zn(β-lactamide) complex **D** reported recently by Brombacher and Vahrenkamp [Scheme 7; $Tp^{Cum,Me}$ = tris(3-cumyl-5-methylpyrazolyl)borate].[40] It should be noted that no other structurally characterized zinc β-lactamide complex has been reported in the literature, and complexes featuring a bridging β-lactamide between other metal ions are very scarce.[41] In **D** the β-lactamide is bound through its N atom to a single zinc ion, while the lactamide O atom remains uncoordinated. This reduces conjugation within the amide moiety and hence leads to lengthening of the C–N bond [1.363(4)/1.356(4) Å in **D** vs. 1.333(2) Å in free 2-azetidinone] and a shortening of the C=O bond [1.214(5)/1.227(4) Å in **D** vs. 1.226(2) Å in free 2-azetidinone]. Binding of a second zinc ion to the β-lactamide O atom, as observed in complexes **3** and **4**, reverses this trend: the C–N bond is shortened [1.274(8)/1.292(7) Å] and the C=O bond is clearly elongated [1.238(7)/1.245(8) Å]. At the same time the N–C–O bond angle of 131.5(5)° (**3**) or 130.9(6)° (**4**) remains unchanged [131.7(4)/131.1(3)° in **D**]. A CSD search reveals that many organic molecules containing a β-lactam subunit have been characterized crystallographically, and both the C=O and C–N bond lengths are found to vary considerably, with most C=O bonds in the range 1.15–1.27 Å (mean value 1.207 Å) and most C–N bonds in the range 1.30–1.45 Å (mean value 1.370 Å). Overall, the lactamide ligand within the dimetallic clamp of **3** and **4** features a relatively long C=O bond and a short C–N bond that is close to the lower limit of the above range.



Scheme 7. C–N and C=O bond lengths of 2-azetidinone,[39] complex **D**,[40] and complexes **3** and **4**.

In line with these structural findings, the β-lactam ν(C=O) stretch in **D** (1709 cm^{-1}) is barely shifted from those of free 2-azetidinone, while the ν(C=O) vibrations of **3** and **4** appear at much lower frequency, as mentioned above. Apparently, changes in the β-lactam unit (and possible activation towards subsequent reactions, such as hydrolysis) differ dramatically depending on whether the β-lactamide is bound to a single or two adjacent zinc ions. Although initial experiments with **3** and **4** did not reveal any activation of the β-lactam ring towards hydrolytic cleavage (as expected due to the anionic character of the *N*-deprotonated species), the present findings once more underline the particular ability of highly preorganized dinuclear scaffolds to accommodate and polarize small substrate molecules within their dimetallic binding pocket, which is distinct from activation at a single metal ion.

Experimental Section

General Remarks: Manipulations were carried out under dry nitrogen by employing standard Schlenk techniques. Solvents were dried according to established procedures. Complexes **1** and **2** were prepared in situ starting from HL^1 and HL^2;[42,43] all other chemicals were used as purchased. Microanalyses: Mikroanalytische Laboratorien des Organisch-Chemischen Instituts der Universität Heidelberg. IR spectra: Perkin–Elmer 983G; recorded as KBr pellets. UV/Vis spectra: Perkin–Elmer Lambda 19. FAB mass spectra: Finnigan MAT 8230.

Caution! Although no problems were encountered in this work, perchlorate salts are potentially explosive and should be handled with proper precautions.

Synthesis of $[L^1Zn_2(C_3H_4NO)](ClO_4)_2$·MeOH (3): A solution of HL^1 (260 mg, 0.50 mmol) in MeOH (30 mL) was treated with 2 equiv. of KO*t*Bu (112 mg, 1.00 mmol) and 2 equiv. of $Zn(ClO_4)_2$·$6H_2O$ (372 mg, 1.00 mmol). After stirring the mixture at room temperature for 30 min, 1 equiv. of 2-azetidinone (36 mg, 1.01 mmol) was added, and stirring continued for 2 h. The reaction mixture was then concentrated to dryness and the residue was taken up in methanol (20 mL) and filtered. Layering of the resulting clear solution with diethyl ether afforded colorless crystals of the product **3**·MeOH at room temperature over a period of several days (320 mg, 67%). MS (FAB+): *m*/*z* (%) = 818 (100) $[L^1Zn_2(C_3H_4NO)(ClO_4)]^+$. IR (KBr): $\tilde{\nu}$ = 3523 (w, CH_{MeOH}), 2973 (m), 2938 (m), 2877 (m), 1606 (s, C=O), 1516 (w), 1468 (m), 1384 (m), 1348 (w), 1331 (w), 1283 (w), 1263 (w), 1225 (w), 1181 (w), 1091 (vs, ClO_4), 970 (m), 909 (m), 818 (m), 795 (m), 778 (m), 734 (m), 622 (s), 546 (w) cm^{-1}. $C_{32}H_{65}Cl_2N_9O_9Zn_2$·MeOH (953.6): calcd. C 41.56, H 7.29, N 13.22; found C 41.10, H 7.13, N 13.43.

Synthesis of $[L^2Zn_2(C_3H_4NO)](ClO_4)_2$·acetone (4): A solution of HL^2 (245 mg, 0.50 mmol) in MeOH (30 mL) was treated with 2 equiv. of KO*t*Bu (112 mg, 1.00 mmol) and 2 equiv. of $Zn(ClO_4)_2$·$6H_2O$ (372 mg, 1.00 mmol). After stirring the mixture at room temperature for 30 min, 1 equiv. of 2-azetidinone (36 mg, 1.01 mmol) was added, and stirring continued for 2 h. The reaction mixture was then concentrated to dryness and the residue was taken up in acetone (20 mL) and filtered. Layering of the resulting clear solution with light petroleum afforded colorless crystals of the product **4**·acetone at room temperature over a period of several days (180 mg, 38%). MS (FAB+): *m*/*z* (%) = 786 (10) $[L^2Zn_2(C_3H_4NO)(ClO_4)]^+$, 307 (100). IR (KBr): $\tilde{\nu}$ = 3108 (w), 3069 (w), 2957 (w), 2904 (w), 2857 (w), 1704 (m, $C{=}O_{acetone}$), 1629 (s), 1606 (s), 1589 (s), 1565 (m), 1504 (w), 1479 (m), 1438 (m), 1378 (w), 1314 (w), 1259 (m), 1218 (w), 1159 (w), 1090 (vs, ClO_4), 1024 (m), 974 (w), 954 (w), 899 (w), 880 (w), 811 (w), 768 (m), 650 (m), 622 (s), 527

Table 1. Crystal data and refinement details for **3** and **4**.

	3	**4**
Empirical formula	$C_{32}H_{65}N_9Cl_2O_9Zn_2$·MeOH	$C_{32}H_{33}N_9Cl_2O_9Zn_2$·acetone
M_r [g mol]	953.61	947.39
Crystal size [mm]	0.44 × 0.32 × 0.26	0.27 × 0.26 × 0.17
Crystal system	monoclinic	monoclinic
Space group	$P2_1/c$	$P2_1/c$
a [Å]	19.4962(15)	17.3710(15)
b [Å]	14.1066(11)	15.5745(14)
c [Å]	16.1861(12)	15.0981(13)
β [°]	102.261(2)	105.685(2)
Volume [Å^3]	4350.0(6)	3932.6(6)
$\rho_{calcd.}$ [g cm^{-3}]	1.456	1.600
Z	4	4
F(000)	2016	1944
Temperature [K]	173(2)	173(2)
λ(Mo-K_α) [Å]	0.71073	0.71073
hkl range	–25 to 25, 0 to 18, 0 to 21	–20 to 19, 0 to 18, 0 to 17
θ range [°]	1.9–28.3	1.8–25.0
Measured reflections	42844	21922
Unique reflections (R_{int})	10734 (0.036)	6946 (0.074)
Observed reflections [$I > 2\sigma(I)$]	8935	4588
Refined parameters	549	529
Residual electron density [e Å^{-3}]	1.56	1.35
R_1 [$I > 2\sigma(I)$]	0.0755	0.0634
wR_2 (all data)	0.1851	0.1931
Goodness-of-fit	1.105	1.060

(w), 502 (w), 487 (w), 415 (w) cm^{-1}. $C_{32}H_{33}Cl_2N_9O_9Zn_2$·acetone (947.4): calcd. C 44.37, H 4.15, N 13.31; found C 43.88, H 4.32, N 12.75.

X-ray Crystallographic Study: Data collection was carried out with a Bruker AXS CCD diffractometer at 173 K using graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å). Structures were solved by direct methods (SHELXS-97) and refined by full-matrix least-squares techniques based on F^2 (SHELXL-97).[44] Atomic coordinates and thermal parameters of the non-hydrogen atoms were refined in fully anisotropic models. Hydrogen atoms were included using the riding model. Some of the ethyl groups in **3** are disordered. Crystal data and refinement details are listed in Table 1. CCDC-258281 (**3**) and -258282 (**4**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgments

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