Novel Marine Sponge Derived Amino Acids. 9. Lithium Complexation of Jasplakinolide

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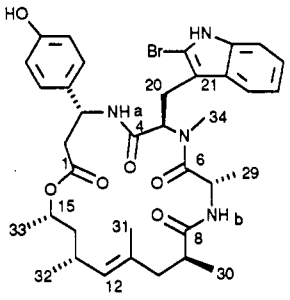
A complexation study was carried out with jasplakinolide (1), a novel mixed polyketide–depsipeptide, and univalent metal ions Li^+, Na^+, and K^+. Li^+ binding was observed with just one of the two major solution conformations of 1. The complex was characterized by NMR and molecular mechanics calculations. This study represents the first report on complexation between a mixed polyketide–depsipeptide and metal ion.

Jasplakinolide[1] (jaspamide)[2,3] (1) was the first macrocyclic mixed polyketide–depsipeptide to be reported from a marine sponge and was the subject of a recent total synthesis.[4] This natural product has notable biological properties including anthelminthic,[1] cytotoxic,[1] selective antimicrobial,[5] insecticidal,[2] and ichthytotoxic[3] activities. Our previous report of the gross structure of 1 was based on analysis of two-dimensional NMR data, and a subsequent conformational analysis study[6] on 1 provided a complete assignment of all NMR resonances. This new



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study also revealed the backbone geometry of 1 was described by two major conformers, $\mathbf{1g}^+$ and $\mathbf{1g}^-$, which differed by ≈120° rotation about the C1–C2–C3–N torsion angle. Models of both conformers revealed a potential cavity for binding with metal ions. Metal complexation of mixed polyketide–depsipeptides have not been explored, in contrast to numerous reports on cyclic depsipeptide ionophores.[7] In order to define the ionophoric potential of 1, we carried out a complexation study of 1 with the univalent metal cations Li^+, Na^+, and K^+ and now report on the complexation of 1 with Li^+.

Results and Discussion

Titration of 1 (70 or 200 mM) with $LiClO_4$ or LiBr, NaSCN, and KSCN in CD_3CN was monitored by ^1H (300 MHz) and ^{13}C (75 MHz) NMR. Significant changes in chemical shifts were only observed in the Li^+ titration. Separate signals were not observed in the ^{13}C spectra for the complexed and uncomplexed forms because of a rapid equilibrium in comparison to the NMR time scale. The ^{13}C chemical shifts of carbonyls C1, C4, and C8 shifted downfield as a function of added Li^+ equivalents, whereas no significant change was seen for C6 chemical shift.[8] This suggests that three-site binding occurred between Li^+ and the oxygens of carbonyls C1, C4, C8. The binding constant (K) for 1:1 macrocycle to cation complexation in CD_3CN (20 °C) was determined from the ^{13}C NMR titration data using standard methods, $K = 60\ M^{-1}$, $\Delta G = -10$ kJ/mol.[9]

The titration of 1 (initial concentration 200 mM in CD_3CN) with Li^+ exhibited several interesting features in the ^1H NMR spectra (Figure 1). Line broadening was observed during the titration (Figure 1b), and the ^1H signals became sharp again at the endpoint (Figure 1c). The broadening results from lithium exchange between jasplakinolide molecules as shown in eq 1.[10] Information

$$1\text{-}Li^+ + 1 \rightleftharpoons 1 + 1\text{-}Li^+ \quad (1)$$

leading to identity of the solution conformation of the 1:1 complex was obtained from the H2/H2′ diastereotopic hydrogens in the ^1H NMR spectra (Figure 1). We have previously shown that the C1–C2–C3–N torsion angle is flexible in 1 by the similar chemical shifts of H2/H2′ ($\Delta\delta$ = 0.08 ppm), the intermediate coupling constants for H2–H3 (4.0 Hz) and H2′–H3 (7.1 Hz), and the similar calculated energies of conformers $\mathbf{1g}^-$ and $\mathbf{1g}^+$.[6] At the endpoint of the Li^+ titration, the H2 and H2′ resonances shift apart ($\Delta\delta$ = 0.28 ppm), and the coupling constants between H2–H3 and H2′–H3 are divergent, 3.6 Hz and 12.0 Hz, respectively (Figure 1c). The extreme difference in coupling values and the increase in the diastereotopic shift difference suggest the C1–C2–C3–N torsion angle is locked into the g^+ conformation (as in $\mathbf{1g}^+$) in the 1:1 complex.

The most expeditious way to determine the solution conformation of this unique but weakly bound 1:1 complex was to employ molecular mechanics calculations by using MACROMODEL. Initially, the metal ion was docked with major solution conformations, $\mathbf{1g}^-$ and $\mathbf{1g}^+$. The cation was introduced near the oxygens of carbonyls C1, C4, and C8 because both conformers have these three carbonyl oxygens located on the same side of the macrocycle plane. Energy minimization was then carried out with the Amber force field with added nonbonded parameters for the metal

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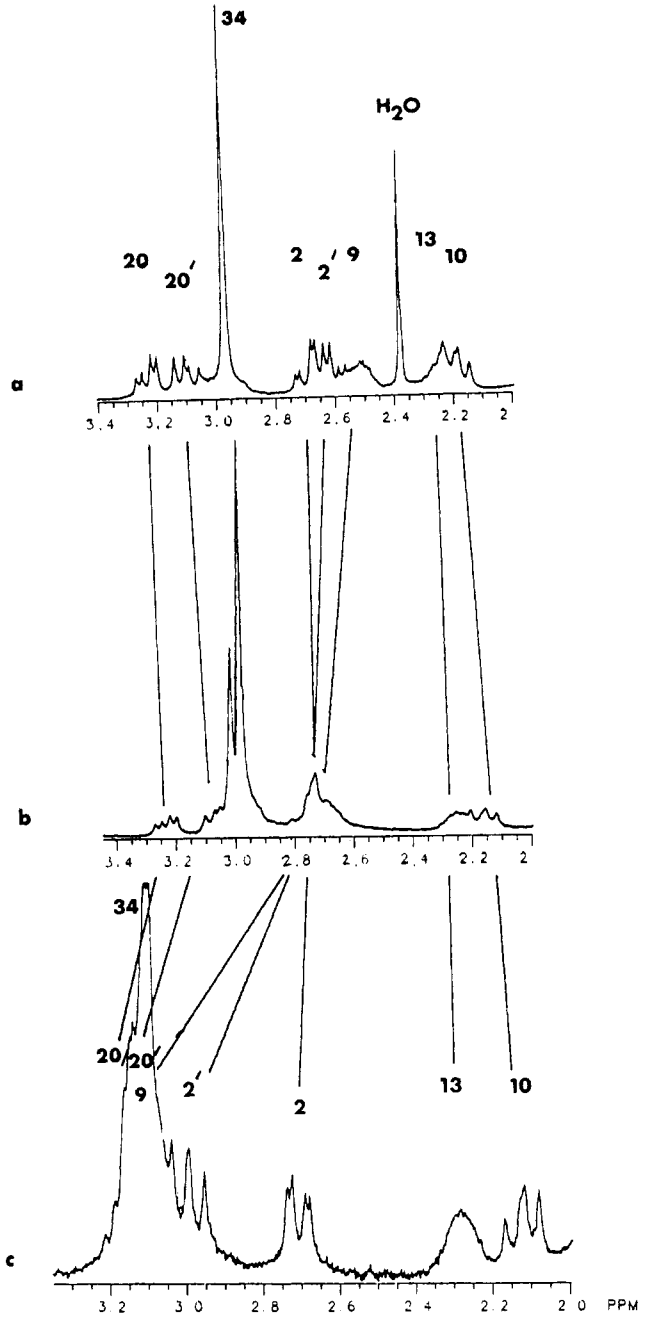

Figure 1. (a) ^{1}H NMR (partial) of 1. (b) 1 + 1 equiv of LiBr; (c) 1 + 6 equiv of LiBr.

and the dielectric in the electrostatic term.[11] Two different conditions having a low and high dielectric were employed. In the first case a gas-phase dielectric with the distance-dependent term, $\epsilon = R_{ij}$,[12] was used and the van der Waals (VDW) radii of Li^+ and Na^+ were varied until the calculated M^+–O bond distances were comparable to measured distances from X-ray structures of known complexes.[7,13] The final VDW radii for Li^+ and Na^+ were 1.3 and 1.6 Å, respectively, and are similar to values reported in previous molecular mechanics calculations of complexes.[14] The low dielectric employed in case 1 caused the electrostatics to be dominant, and a large VDW radius for the metal was needed to offset this effect. The second case utilized a constant dielectric, $\epsilon = 36$, similar to the dielectric constant of acetonitrile, along with the actual VDW radii for Li (0.67 Å) and Na (0.97 Å).[15] Electrostatics were not a dominant factor due to the high dielectric and the actual VDW radii for the metals generated reasonable M^+–O bond lengths.

Minimization results of the initially docked structures indicated that three-site binding only occurred between the cation and the oxygens of carbonyls C1, C4, and C8 in $\mathbf{1g}^+$ and not in $\mathbf{1g}^-$.[16] The summary of calculated energy values for case 1 and case 2 appear in Tables I and II, respectively. The relative cation binding affinities were determined by taking the difference between the complexation energies for Li^+ and Na^+ (case 1: $\Delta\Delta E = -53.7$ kJ/mol, case 2: $\Delta\Delta E = -14.0$ kJ/mol). Results from both cases predict that a cation specificity exists for Li^+, but the results of case 2 (Table II) are closer to the experimental observations. In particular, the ΔE for Na^+ complexation of approximately 0 kJ/mol is in agreement with the experimental observation that Na^+ does not bind to 1. Furthermore, the smaller ΔE in case 2 for Li^+ also agrees with the weak experimental binding constant. Mechanics calculations indicate the preference of Li^+ over Na^+ binding with $\mathbf{1g}^+$ is due to the metal–ligand interaction energy (ΔE_{ML}) and not the strain energy (ΔE_S). ΔE_S,

Table I. Total and Interaction Energies for Li^+ and Na^+ Complexes with $\mathbf{1g}^+$[a]

molecule	E_T[b]	ΔE[c]	ΔE_S[d]	ΔE_{ML}[e]
$\mathbf{1g}^+$	−70.9			
Li^+–$\mathbf{1g}^+$ = **2A**	−210.5	−139.6	65.0	−204.6
Na^+–$\mathbf{1g}^+$	−156.8	−85.9	68.6	−154.5

[a] Energies (kJ/mol) calculated with $\epsilon = R_{ij}$, Li VDW radius = 1.3 Å, Na VDW radius = 1.6 Å. [b] Total energy. [c] Complexation energy, $M^+ + \mathbf{1g}^+ \rightleftharpoons M^+/\mathbf{1g}^+$. [d] Strain energy induced in the host due to metal–host interaction. ΔE_S was calculated by freezing the complex, removing the ion, calculating the energy, and then subtracting the minimized $\mathbf{1g}^+$ energy. [e] Metal–ligand (ML) interaction energy, $\Delta E_{ML} = \Delta E - \Delta E_S$.

Table II. Total and Interaction Energies for Li^+ and Na^+ Complexes with $\mathbf{1g}^+$[a]

molecule	E_T	ΔE	ΔE_S	ΔE_{ML}
$\mathbf{1g}^+$	29.9			
Li^+–$\mathbf{1g}^+$ = **2B**	15.5	−14.4	14.4	−28.8
Na^+–$\mathbf{1g}^+$	25.5	−0.4	15.4	−15.8

[a] Energies (kJ/mol) calculated with $\epsilon = 36$, Li VDW radius = 0.67 Å, Na VDW radius = 0.97 Å.

Table III. Summary of Calculated Li^+–O Bond Lengths

	2A[a]	**2B**[b]
bond lengths (Å)		
C_1O–Li	2.103	2.146
C_4O–Li	2.069	2.156
C_6O–Li	3.685	2.642
C_8O–Li	2.041	2.040

[a] $\epsilon = R_{ij}$, Li VDW radius = 1.3 Å. [b] $\epsilon = 36$, Li VDW radius = 0.67 Å.

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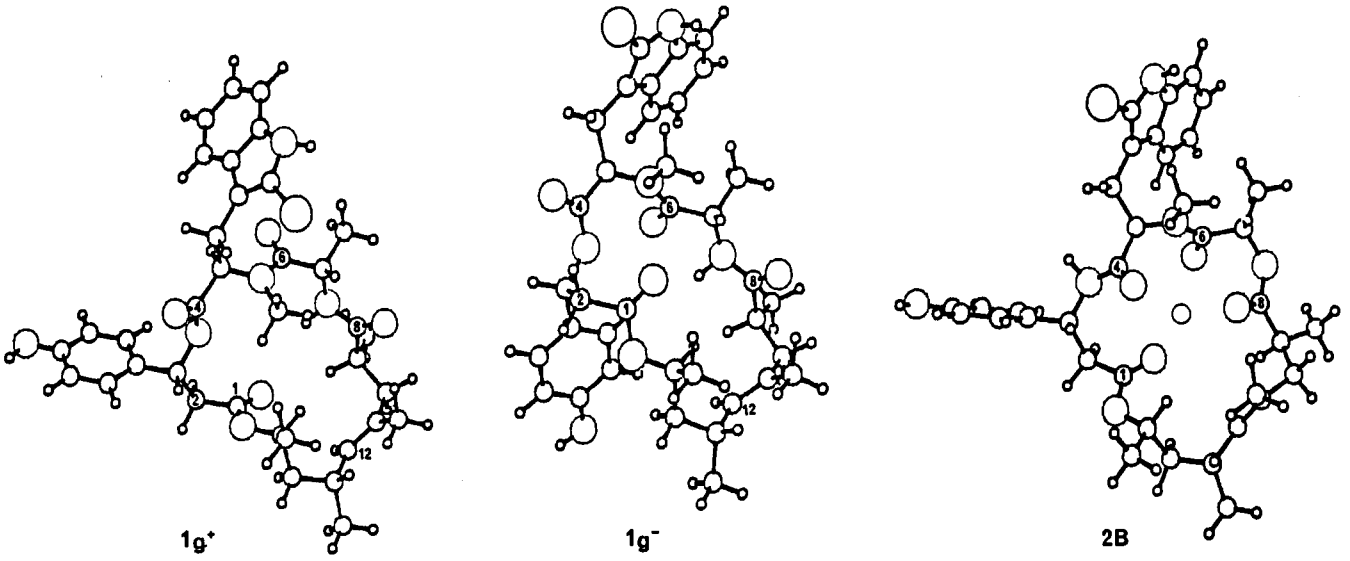

Figure 2.

Table IV. Summary of Calculated and Observed Coupling Constants (Hertz)

	2A[a]	2B[b]	observed
J_{2-3}	10.5	11.6	12.0
$J_{2'-3}$	1.2	2.1	3.6
J_{Ha-3}	7.8	7.8	9.0
J_{Hb-7}	4.9	3.8	6.6
J_{9-10}	12.3	12.3	11.4

[a] $\epsilon = R_{ij}$, Li VDW radius = 1.3 Å. [b] $\epsilon = 36$, Li VDW radius = 0.67 Å.

the amount of energy needed for reorganization of $\mathbf{1g}^+$ to form a complex with Li^+ or Na^+ are similar in both cases (Tables I and II). Thus, the important factor that controls the Li^+ specificity for $\mathbf{1g}^+$ is the larger metal–ligand energy (ΔE_{ML}) for Li^+ versus Na^+ (Tables I and II).

The geometry of the Li^+ complex predicted from both cases were different and correspond to the VDW radius used in the minimization. Case 1 and case 2 generated the complex conformations **2A** and **2B** (Figure 2), respectively. Their major difference is the position of Li^+ relative to the macrocycle, and only **2B** is arbitrarily shown here. The calculated Li^+–O bond lengths for **2A** and **2B** are shown in Table III. It is noteworthy that the three normal Li^+–O bonds are approximately 2.0–2.1 Å, but a long Li^+–O bond is predicted for the oxygen of carbonyl C6. The position of the Li^+ atom was nested in **2A**, lying above the macrocycle plane, because of the larger VDW radius used for Li^+ (case 1). When the actual VDW radius for Li^+ was used (case 2), the Li^+ atom was located in the plane of the macrocycle in **2B**. The calculations from both cases supported the NMR assignments, i.e., three-site binding between Li^+ and the oxygens of carbonyls C1, C4, and C8 with the C1–C2–C3–N torsion angle in the metal complex locked into the g^+ conformation, which can be seen by comparing $\mathbf{1g}^+$ and **2B**. The calculated coupling constants for **2A** and **2B** are shown in Table IV and compare favorably to the measured values.

The binding constant of the Li^+–jasplakinolide 1:1 complex[17] is much smaller in comparison to reported binding constants for hexadepsipeptides such as the enniatins. It is interesting to note that only the $\mathbf{1g}^+$ conformation of 1 binds to Li^+ due to less reorganization required for binding in comparison to $\mathbf{1g}^-$. While many neutral molecules have been explored by the combination of ^1H NMR analysis and molecular mechanics, this study adds to an emerging list in which this technique has been applied to probe structural properties in a charged complex.[13,18]

Experimental Section

Jasplakinolide (1) was isolated as previously described.[1] NMR spectra were recorded on a GN-300 spectrometer (300 MHz for ^1H and 75 MHz for ^{13}C). LRFABMS data were obtained at the UC Berkeley mass spectrometry lab.

Titration. Titrations of 1 (70 or 200 mM in CD_3CN) with LiBr, $LiClO_4$, NaSCN, and KSCN in CD_3CN were monitored by ^1H and ^{13}C NMR spectroscopy. The ^{13}C NMR shifts of C1, C4, and C8 were used to calculate the binding constant, K, shown in eq 2,[9]

$$K = \alpha/[(1 - \alpha)(b_0 - c_0\alpha)] \quad (2)$$

$$\alpha = \Delta\delta/\Delta\delta_{max} \quad (3)$$

where α is the degree of complexation, c_0 is the initial concentration of 1, and b_0 is the concentration of salt. The binding constant was calculated with points within the region $0.6 < \alpha < 0.9$. Similar binding constants, $K = 63 \pm 16\ M^{-1}$ (rms), $60 \pm 14\ M^{-1}$, were obtained with C1 and C8 ^{13}C shifts, whereas $K = 157 \pm 23\ M^{-1}$ was calculated with C4.

Li^+ Complex ($\mathbf{1g}^+$–LiBr): ^{13}C NMR (CD_3CN, 75 MHz, δ in ppm, atom number) δ 173.2 (C1), 41.8 (C2), 50.5 (C3), 170.4 (C4), 57.2 (C5), 174.5 (C6), 46.8 (C7), 177.1 (C8), 40.3 (C9), 42.4 (C10), 134.2 (C11), 129.7 (C12), 30.1 (C13), 43.4 (C14), 72.0 (C15), 132.5 (C16), 128.3 (C17), 116.3 (C18), 157.4 (C19), 25.3 (C20), 110.3 (C21), 128.3 (C22), 119.4 (C23), 120.5 (C24), 122.8 (C25), 111.7 (C26), 137.4 (C27), 109.9 (C28), 18.5* (C29), 19.3* (C30), 18.9* (C31), 22.0 (C32), 19.8* (C33), 32.5 (C34), (*) interchangeable.

Computational Methods. Computer modeling was carried out with the MACROMODEL program (version 1.5) on a Vax 11/750 computer with an Evans and Sutherland (PS 330) picture system. Molecular mechanics calculations were performed with the Amber force field with a distance-dependent dielectric or constant dielectric. Structures were energy minimized with the Block Di-

(17) It is important to point out that 1 forms a higher order jasplakinolide–LiBr complex (possibly 2:1) having the following general properties: empirical formula $C_{72}H_{90}N_8O_{12}Br_3Li$ obtained from [LRFABMS]; mp 216–220 °C versus 1, mp = 177–190 °C, decomposes above 200 °C. It was prepared by the addition of 0.5 equiv of LiBr to a 200 mM solution of 1 in acetonitrile and isolated as a precipitate.

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agonal Newton Raphson algorithm in Cartesian coordinate space until the rms energy gradient was less than 0.04 kJ/mol Å. Vicinal coupling constants (^3J) in the candidate conformations were calculated in MACROMODEL with the appropriate coupling equation for peptide[19] and aliphatic[20] dihedral angles.

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The Structure and Conformational Properties of a Cembranolide Diterpene from *Clavularia violacea*

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The structure of a new cembranolide, pachyclavulariolide (**2**), isolated from the octocoral *Pachyclavularia violacea*, was determined by extensive 2D NMR experiments. The relative stereochemistry at each of six chiral sites in **2** was assigned by using ROESY correlations, ^3J coupling constants, and molecular mechanics calculations. Results from the conformational analysis of **2** indicated that one major conformation exists in solution and corresponds to the global minimum predicted by molecular mechanics calculations. This report represents the first detailed solution conformational analysis study of a cembrane ring.

In comparison to the other major orders within the octocorals the Stoloniferia are sparse inhabitants of coral reefs, yet they are a source of a rich array of metabolites.[1] The stoloniferan families of chemical importance are the Tubiporidae (including the genera *Tubipora*), and the Clavulariidae (including the genera *Clavularia* and *Pachyclavularia*). Novel furanocembranoids **1a–c** have been previously isolated from *Pachyclavularia*.[2] By contrast, the chemistry of *Tubipora* or *Clavularia* includes norsesquiterpenes,[3] unusual sesquiterpenes,[4-6] bicyclic diterpenes,[7,8] unique prostanoids,[9] or highly oxygenated steroids.[10] Our investigation of *p. violacea* from Vanuatu[11] yielded a new cembranolide, pachyclavularolide (**2**), which is related to pachyclavulariadiol (**1a**) except that the furan ring has been oxidized to a butenolide. In this report we illustrate the effective combination of NMR and molecular mechanics calculations to provide the complete stereostructure and an understanding of the conformational properties of this new cembranolide.

Results and Discussion

The diterpenoid nature of **2** was indicated by the partial molecular formula of $C_{20}H_{28}$ established from a ^{13}C APT NMR spectrum, the presence of four methyl groups, and the complete formula of $C_{20}H_{30}O_5$ from a LREIMS (M^+ = 350). The unsaturated functionalities evident from NMR and IR spectra were an α,β-unsaturated ester (1750 cm^{-1}, δ 175.1 ppm/C16, 165.2/C1, 124.5/C15, 80.2/C2) and one trans-trisubstituted double bond (δ 130.0/C4, 131.0/C5, 16.6/C18); consequently, a tricyclic structure was apparent. Additional functionality included a vicinal diol (δ 76.2/C13, 68.2/C14) with two exchangeable hydrogens, and a scalar correlation was observed between H13 and H14 in a 500-MHz ROESY spectrum; however, $J_{13-14} \approx 0$ Hz. The 1,2-diol relationship in **2** was also established by the conversion of **2** to the dioxolane **3**. Consequently, the single remaining unaccounted oxygen and two oxygen-

Table I. NMR COSY Data for Pachyclavularolide (2)

^1H–^1H regular	^1H–^1H long range	^{13}C–^1H long range (J = 9 Hz)
H2-H3,H3′	H2–H17	C1–H2,H3,H3′,H13,H14,H17
H3–H3′	H3–H5,H18	C2–H3,H3′,H14
H5–H6/H6′	H5–H18	C3–H2,H5,H18
H6/6′–H7,H7′	H14–H17	C4–H2,H3,H3′,H6/6′,H18
H7–H7′		C5–H3,H3′,H6/6′,H7,H18
H7′–H8		C6–H5,H7,H8
H8–H9,H19		C7–H5,H6/6′,H9,H19
H9–H10,H10′		C8–H6/6′,H7,H19
H10–H10′,H11′		C9–H7,H8,H10′,H11,H19
H10′–H11,H11′		C10–H11,H11′
		C11–H10,H13,H20
		C12–H11′,H13,H20
		C13–H11,H11′,H14,H20
		C14–H13
		C15–H2,H14,H17
		C16–H2,H17

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