A Multinuclear Ca^{2+} Complex of a Linear N-Protected Glycyl-Dipeptoid Derivative

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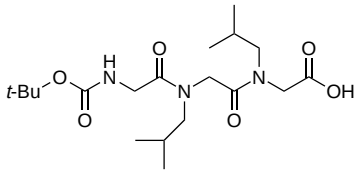
Divalent cations such as Mg^{2+} or Ca^{2+} are known to be important in modulating the binding affinity of hormones such as oxytocin,[1−3] vasopressin,[1,2,4,5] gastrin,[6] glucagon,[7,8] GnRH,[9] insulin,[10] substance P,[11] and bombesin.[12] The receptors[13] of these hormones are also known to bind Ca^{2+}. Complexation of linear peptides to Ca^{2+} cations in solution has been studied by a variety of techniques, such as CD, NMR, and IR spectroscopies. To date, only two crystal structures of Ca^{2+} complexes with peptides have been reported and both of these crystal structures are of cyclic peptides.[14,15] In c(Ala-Leu-Pro-Gly)$_2$·Ca(ClO$_4$)$_2$,[14] complexation occurs through an incomplete encapsulation of the metal ion by the peptide molecule, and in c(Pro-Gly)$_3$·Ca(ClO$_4$)$_2$,[15] a complete encapsulation is found and two cyclic peptide molecules sandwich a Ca^{2+} ion. Solvent molecules occupy coordination sites in both of these crystal structures.

We have recently been involved in the preparation of new building blocks for collagen-like structures using peptidomimetic residues such as *N*-isobutylglycine (Nleu).[16,17] As part of our program we have synthesized Boc-Gly-Nleu-Nleu-OH (**1**) and discovered that its ionized form complexes calcium ions. We report here the first crystal structure of a calcium complex of a linear peptide-like structure. The structure of $Ca^{2+}{}_3$(Boc-Gly-Nleu-Nleu-O$^-$)$_6$ (Figure 1) was determined by single-crystal X-ray diffraction techniques.[18] The calcium cations are completely encapsulated through oxygen atoms of the N-protected glycyl−dipeptoid derivative (Figure 2) without any involvement of solvent molecules, although they are present in the unit cell. This paper also describes an extensive analysis of the conformation of the Nleu peptoid residue. The conformation of the glycyl−dipeptoid molecule is presented in Figure 3.



(1)

In $Ca^{2+}{}_3$(Boc-Gly-Nleu-Nleu-O$^-$)$_6$, each glycyl−dipeptoid unit occupies a folded conformation and behaves as a bischelate toward a lateral calcium ion. The folding of the backbone chain, which results in coordination to the divalent cation, is made possible because of the *cis* conformation of the two tertiary amide linkages involving Nleu peptoid residues. All six

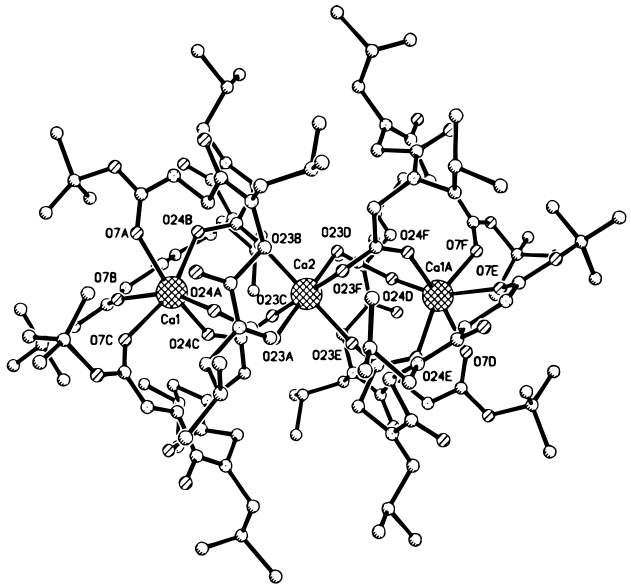


Figure 1. The $Ca^{2+}{}_3$(Boc-Gly-Nleu-Nleu-O)$_6$ entity. Calcium ions and oxygen atoms are represented as hatched and crossed circles, respectively. The central calcium ion is positioned on a center of symmetry.

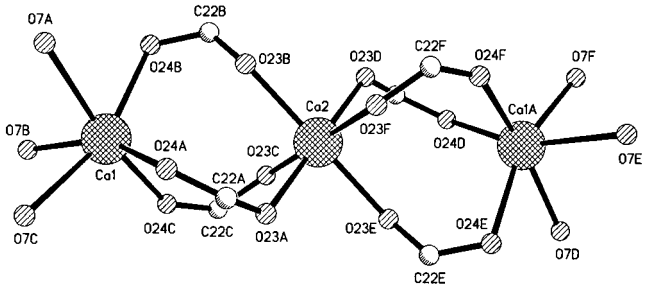


Figure 2. Oxygen coordinations to Ca^{2+} ions.

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(18) Crystals of $Ca^{2+}{}_3${Boc-Gly-Nleu-Nleu-O$^-$}$_6$·3CH$_3$CN were grown from acetonitrile solutions. Solvent molecules are not shown in Figure 1. For $C_{57}H_{102}N_9O_{18}Ca_{1.5}$·3CH$_3$CN, FW = 1384.77, monoclinic $P2_1/n$, a = 17.320(8) Å, b = 17.802(10) Å, c = 26.693(9) Å, β = 97.47(3)°, Z = 4, 10 757 unique reflections, 3° < 2θ < 45°, R = 0.0941 for 6429 reflections with $F_o \geq 4.0\ \sigma(F_o)$. All intensity measurements were recorded at 193 K, using graphite-monochomated Mo Kα radiation (λ = 0.710 73 Å) at a variable rate ω scan technique. The structure has been solved by direct methods and refined by full-matrix least squares. All calculations were performed using SHELXTL PLUS programs.

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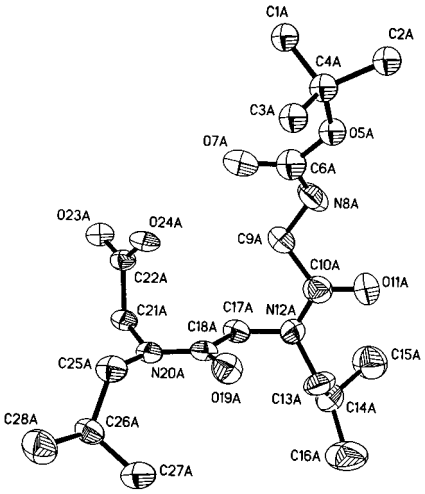

Figure 3. The structure of one Boc-Gly-Nleu-Nleu-O^- unit.

independent N-protected trimer molecules have nearly the same conformation, and the C-terminal groups exist as carboxylate anions in the crystal structure. Each trimer molecule acts as a bidentate ligand toward one lateral calcium cation, which coordinates one oxygen of the carboxylate group as well as the urethane carbonyl oxygen. The coordination at the bivalent ion resembles an octahedral complex. The trimer units are able to complex the central calcium ion through their second carboxylate oxygens. The central calcium ion is therefore coordinated to all six glycyl−dipeptoid units. The central calcium ion sits on the center of symmetry so that the resulting globular entity is centrosymmetric with one half of it consisting of structures of right-handed helicity and the other half consisting of structures of left-handed helicity. This arrangement is made possible because of the achiral nature of the three residues in each peptoid containing trimer. The globular entity, $Ca^{2+}{}_3$(Boc-Gly-Nleu-Nleu-O^-)$_6$, is rather hydrophobic on the surface where the methyl groups of the Boc termini and the isobutyl side chains are located. The charged carboxylate oxygen atoms are positioned in the central core of the globular complex. The central Ca^{2+} ion on the average shows Ca−O distances of 2.20 Å, while the lateral Ca^{2+} ion shows Ca−O distances of 2.35 and 2.38 Å with carboxylate and carbonyl oxygens, respectively.

The three independent achiral molecules coordinated to the lateral calcium ions have very similar conformational angles φ, ψ, and ω: Gly[1] (≈180°, ≈180°, ≈0°), Nleu[2] and Nleu[3] residues (≈−70°, ≈180°, ≈0°) corresponding to right handedness. The centrosymmetric related molecules on the other side of the central calcium ion have opposite handedness with opposite conformational angles. The urethane and the two amide bonds along the chain are in a *trans*, *cis*, and *cis* conformation, respectively, with considerable deviation from planarity. Four of the six side chains of the independent Nleu peptoid residues have χ^1 and χ^2 values near −110° and 60° (and 180°) while the remaining two exhibit the opposite values [110° and −60° (and 180°)]. The observed conformation of the Nleu peptoid residues corresponds to the minimum-energy conformation *cis* α_D form found by others in *ab initio* calculations.[19] The *trans* conformation of the φ and ψ angles allows for the onset of the intramolecular N−H···C═O hydrogen bond between the N−H and the C═O groups of the Gly residue (C_5 conformation), which are not involved in other intermolecular H-bond interactions. Hydrophobic intermolecular interactions allow for the packing of the $Ca^{2+}{}_3${Boc-Gly-Nleu-Nleu-O^-}$_6$ globular entities in the crystal.

We believe that this calcium complex with novel glycyl−dipeptoid ligands, each possessing three oxygen coordination sites, could have applications in coordination chemistry and also for the design of new calcium ionophores by which the mechanism of ion transport through membranes can be probed.

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Supporting Information Available: Experimental details of the synthesis of $Ca^{2+}{}_3$(Boc-Gly-Nleu-Nleu-O^-)$_6$; data collection and refinement details, listings of atomic coordinates, thermal parameters, bond lengths, and bond angles (14 pages). See any current masthead page for ordering and Internet access instructions.

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