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Self-Assembly of C_3 Symmetric Rigid Macrolactams into Very Polar and Porous Trigonal Crystals

Thomas Marmin,[a] and Yves L. Dory*[a]

Abstract: Cyclohexane and cyclotri-β-alanyl have been used as scaffolds for the design of novel C_3-symetric rings incorporating conjugated alkenes and dienes. All three C_3-symmetric lactams share the same triangular shape and their crystal system is trigonal. They all belong to the R3 space group, R3m, R3 and R3c respectively for the increasingly large 12-, 18- and 24-membered rigid rings. All lactams stack on top of each other, through H-bonds and van der Waals non-covalent interactions, leading to endless supramolecular cylinders and tubes. The largest member of the family leads to tubes, whose central pore is wide enough to let water in. A common feature of all the lactams is their very large dipole, of around 9 D according to DFT calculations. Surprisingly, all the resulting cylinders and tubes pack side by side in the crystals, with all the dipoles pointing to the same direction. As a result, all three crystals are anisotropic and appear to be the first members of a new kind of highly polar crystals.

Several works have sought to clarify whether the strong electric dipole of α-helices influences their arrangement inside the proteins. [1,2] The question is legitimate when one observes a ribonuclease inhibitor (Fig. 1a), whose all sixteen α-helices see their dipoles aligned in the same direction. [3] Beside these fundamental considerations, it would be highly desirable to pack α-helices, or related objects, in the same way to create crystals or materials with strong permanent dipoles. [4-7] The helical structure is also very interesting since it can be used as a base for the synthesis of nanotubes, while mimicking gramicidin A. [8,9] However, this approach lacks the modular characteristic of supramolecular chemistry. [10] Nevertheless, some chemists took up the challenge by creating nanotubes by stacking macrolactams (Fig. 1b). [11] This approach is truly versatile and many cyclo-octapeptides constituted of residues of alternating chirality have shown the ability to form trans-membrane channels. [12,13] These cyclo-octapeptides are comparable to cyclic β-sheets, whose amides orient their dipoles perpendicularly to the plane of the macrocycle (Fig. 1c). [14] Of course, this geometry is ideal to allow the formation of the hydrogen bridges responsible for the tubular stack. It is however notable that the tubes formed are devoid of electric dipole unlike α-helices.

We present here how we have succeeded in synthesizing cyclic peptides of a novel genus and presenting strong dipoles (Fig. 1d). By a hierarchical process, we have been able to transfer the dipole of the monomers to the infinite nanotubes of which they are composed. [10,15] We have even continued this phenomenon of amplification of the dipoles to monocrystals, in principle ferroelectric. [16,17]

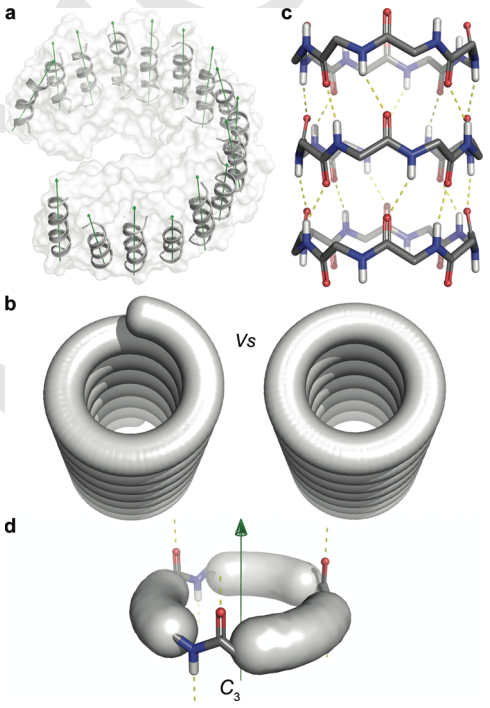

Figure 1. From α-helices to supramolecular polar nanotubes. a. The 16 parallel α-helices of the ribonuclease inhibitor. **b**. A helix and an equivalent supramolecular nanotube obtained through a modular self-assembly process. **c**. Section of a non-polar supramolecular tube constituted of cyclo-octapeptides (side chains and non-polar hydrogen removed for clarity). **d**. Design of a polar C_3-symmetric macrolactam destined to self-assemble as endless very polar nanotubes, through backbone–backbone H-bond interactions and van der Waals contacts. The sausage-like regions are meant to impart rigidity to the ring and to hold the amides in the adequate parallel crown conformation.

α-Helices have 3.6 residues per turn and the amides are all oriented in the same direction. It is of course impracticable to respect this arrangement with cyclo-peptides, since they necessarily consist of an integer number of residues. On the other hand, cyclotri-β-alanyl, formed of three β-amino acid residues, [18,19,20] can mimic the 3_{10}-helix (three residues per turn). [20] This simple molecule, **1**, has already been created and it stacks in the form of infinite nanotubes (Fig. 2a). [21-23] Its three amides are oriented parallel to one another, so that the dipole moment (μ) of macrocycle **1** should approach 10 D, corresponding to three amides (Table 1). [24] Indeed, the dipole moment calculated by DFT method is 9.3 D. [25-27] Thus, the supramolecular

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nanotubes of which they are formed also possess a permanent macro-dipole like 3_{10}- and α-helices. [19]

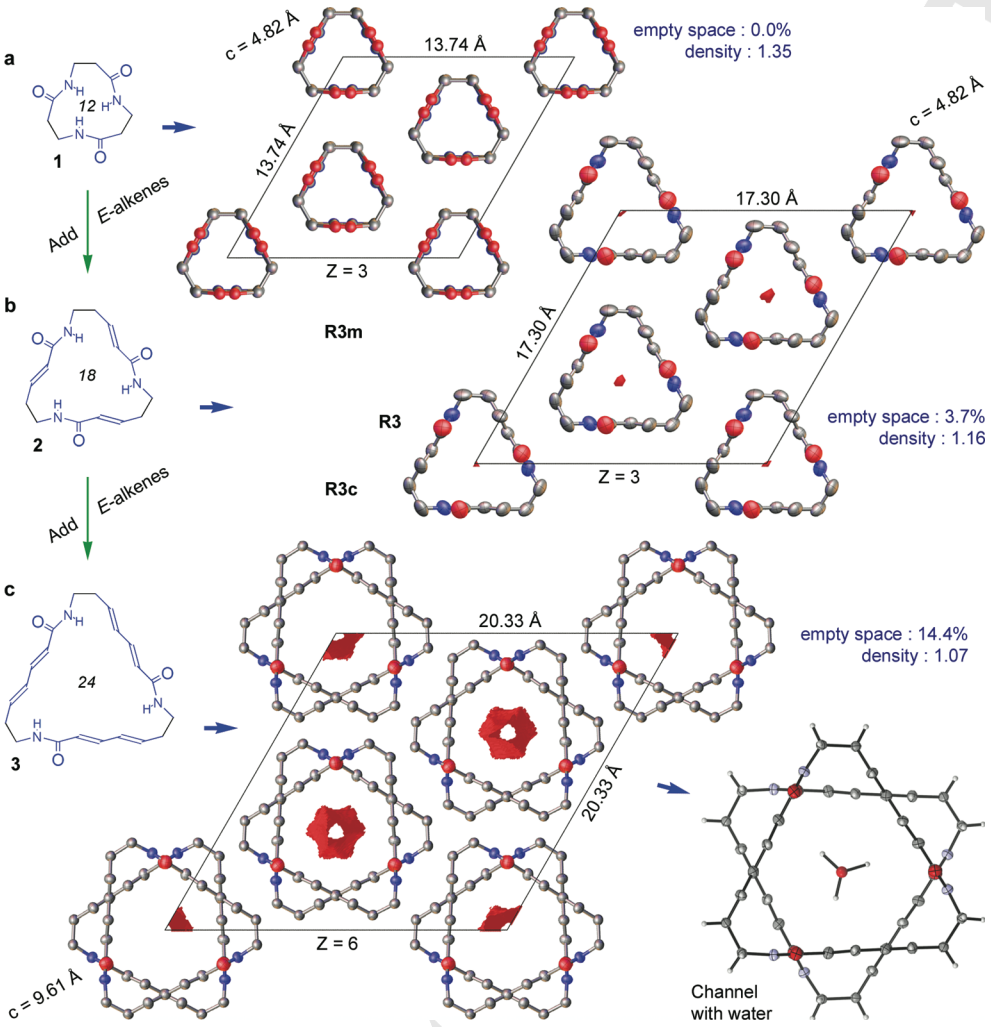

Figure 2. A family of rigid triangular lactams of increasing size and crystallizing in the trigonal system as ferroelectrics. a. The medium ring lactam **1** crystallizes in the R3m space group. Its three gauche ethanes (like in chair cyclohexane) control the entire conformation of the 12-membered triangle. There is no space for guests. **b**. The 18-membered lactam **2**, obtained by adding three rigid conjugated *E*-alkenes to **1**, crystallizes in the R3 space group. Although there is now some available free space (3.7%), it is likely not sufficient to accommodate large guests. **c**. Addition of three conjugated *E*-alkenes to ring **2** leads to the 24-membered large triangular macrolactam **3**, that crystallizes in the R3c space group. The void space, as parallel channels, reaches 14.4% of the whole solid and is large enough to incorporate water molecules (bottom right picture).

The stack is directed by three hydrogen bridges between each pair of macrolactams and by a very favorable dipole alignment, which optimizes the Keesom interactions. [28] It is also very probable that the stability of the tubular edifice is further increased by the cooperativity which usually develops when several peptide bonds form tapes of hydrogen bonds. [29,30] On the other hand, what is very surprising and counterintuitive is the packing of the nanotubes in the crystal, since all the tubes are parallel. [2,4,5] As a result, all the dipoles are aligned and lead to a polar crystal having an enormous macro-dipole.

Table 1. Dipole moments of Rings **1**-**3** and AcNHMe.

Method	Ring **1**	Ring **2**	Ring **3**	AcNHMe
DFT B3LYP	9.31 D	9.03 D	8.81 D	3.77 D
DFT M06-2X	9.33 D	8.77 D	8.57 D	3.78 D
Experimental	/	/	/	3.71 D

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The resulting crystal has all the characteristics of a ferroelectric material. [16,17,31] It is remarkable that all the information stored in each molecule **1** is transferred into the crystal. The crystal system is trigonal and the space group is R3m, perfectly reflecting the C_3-symmetry of **1**.

Properly speaking, cyclotri-β-alanyl **1** does not really form a nanotube, because there is no space available inside to accommodate any molecule whatsoever (Fig. 2a). [32] We have sought to design molecules that would have all the characteristics of **1**, while offering the possibility of assembling as tubes rather than cylinders. It was therefore necessary to increase the size of the sides of molecule **1**, while preserving its rigid triangular shape. We have found that the addition of alkenes conjugated with the carbonyl group can keep the linearity of the sides. The idea was to retain three gauche ethane bridges at the corners, as in cyclohexane and **1**, to lock the desired threefold-symmetry (Fig. 3).

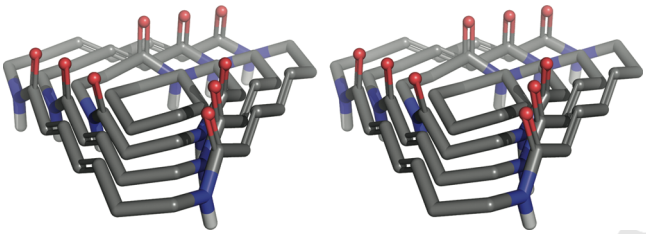
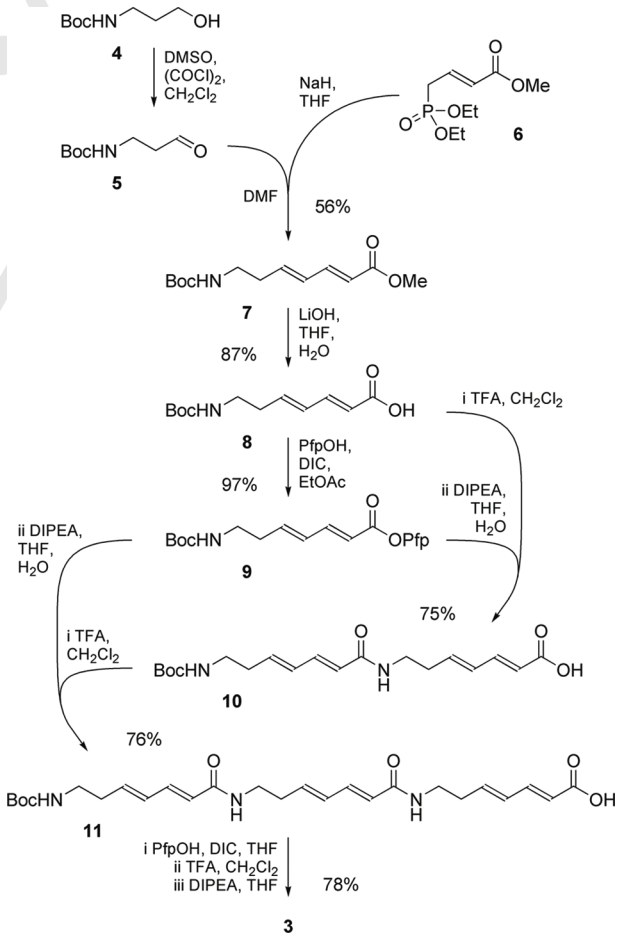


Figure 3. Structural relationships between cyclohexane, 1, 2 and 3. From center to periphery, cyclohexane, **1**, **2** then **3** are shown in wall-eye stereo. Successive symmetrical insertions of three amides, three conjugated alkenes then another three conjugated alkenes to chair cyclohexane, lead to lactams **1**, **2** then **3** respectively.

All these constraints naturally led us to molecule **2**, which we synthesized efficiently (Fig. 2b). [33,34] Molecule **1** is a small 12-membered macrocycle, while its larger counterpart **2** has 18 heavy atoms in the ring. This new macrolactam is perfectly triangular, its three flat sides, described by the seven heavy atoms of each CH_2-CH=CH-CO-NH-CH_2 region, are practically orthogonal to the mean plane of the macrocycle, ensuring the correct orientation of the amides for their stacking by hydrogen bonds. Macrolactam **2** has the same characteristics as its parent **1** and it also stacks as an infinite triangular prism. The dipole of each nanotube must also be very strong because the calculated dipole for monomer **2** is still 9.0 D. In the crystal, all the nanotubes are parallel, although this arrangement is theoretically unfavorable. [2,4,5,28] A notable difference appears with respect to chirality. Of course, neither **1** nor **2** are chiral, on the other hand each monocrystal formed from **2** is endowed with supramolecular chirality (Fig. 3b). [35] All macrolactams have exactly the same shape and orientation in the crystal. This is not the case for **1**; each triangular prism is homochiral as expected, but their packing is then random, leading to a globally racemic crystal. The crystal system for **2** is still trigonal and with the space group R3. As regards the space available inside the nanotubes, it is still very small, being only 3.7% (solvent accessible volume calculated with a spherical probe, 1.4 Å in radius), [32] which is not sufficient to incorporate guest molecules.

In order to achieve a sufficient cavity size, another conjugated double bond was added. The new macrolactam **3** of C_3-symmetry now contains three flat dienamide systems which stiffen the sides (Fig. 2c). [36] The size of the cycle has increased to 24 atoms and its calculated dipole moment is still high with 8.8 D. Having more or less the same characteristics as macrolactam **2**, if not of the size, one could therefore suppose that the behavior could be similar. The synthesis, adapted from the preceding ones, [34] confirmed how easy the macrocyclization of this kind of molecule is (Scheme 1). It should be mentioned that macrolactams **2** and **3** are totally devoid of transannular interactions, which are often serious impediments during ring closure reactions. [37,38] The synthesis of the linear tripeptide **11** follows a straightforward six-step sequence starting from the alcohol **4** (overall yield: 27**%)**. [39] The aldehyde **5**, obtained by Swern oxidation of the alcohol **4**, was reacted with the phosphonate **6** [40] in a Wadsworth-Emmons reaction to produce the diene **7** (56% yield from **4**). [41] Its hydrolysis gave the corresponding acid **8** (87%), that was subsequently activated as its pentaflurophenyl (Pfp) ester **9** (97%). [34,42] Coupling of the free amine, resulting from Boc (butoxycarbonyl) cleavage of **8**, with the Pfp ester **9** afforded the dimer **10** (75%). In the same way, the linear trimer **11** was obtained by coupling the dimeric amine (after Boc cleavage of **10**) to the same activated ester **9** (76%).



Scheme 1. Synthesis of the macrolactam **3**.

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Activation of the acid of **11** (Pfp ester), then cleavage of the Boc protecting group yielded the corresponding TFA (trifluoroacetate) salt, which cyclized readily (78%) upon addition of DIPEA (diisopropylethylamine). [34]

The crystallization, carried out by slow evaporation of the solvent from a solution of **3** in *n*-butanol, gave several crystals favorable to the resolution by X-rays. [43] The crystal system is once again trigonal and the space group is R3c. The stacking by hydrogen bridges and by alignment of dipoles is present, but the form of infinite triangular prism, as observed for **1** and **2**, is lost. Seen along the C_3-axis of the macrolactams, the stack appears in the form of a perfect David star (Fig. 2c). [44] Since this is an alternating stack of enantiomers, there is therefore no supramolecular chirality. [35] This time again, all the nanotubes are oriented in the same direction; the resulting crystal is therefore highly anisotropic. The voids in the crystal are best described as pores, occupying as much as 14.4% of the total volume (Fig. 3c). [32] The nanotubes are therefore truly hollow and, like Gramicidin A, [9] they can accommodate molecules such as water, of which a certain quantity is found in the crystal. Each channel passes through the crystal from edge to edge, along the polar axis c. [6]

In an attempt to explain the reason why all the nanotubes formed from compounds **1**-**3** naturally aligned, we paid particular attention to the geometric characteristics of the three crystals. The resemblances are really striking (Figs. 2-4). For example, the crystals are all trigonal (R3m, R3 and R3c respectively for **1**, **2** and **3**), with increasing lengths for the side a of the unit cell (13.74 Å, 17.30 Å, and 20.33 Å). With respect to the polar axis, the characteristics of the three crystals are nearly identical. [6] In fact, along each nanotube, there is a macrolactam every 4.81 Å on average (**1** and **2**: c = 4.82 Å, **3**: c / 2 = 4.80 Å, its unit cell contains two macrocycles stacked along c, rather than one for **1** and **2**). [19,45,46]

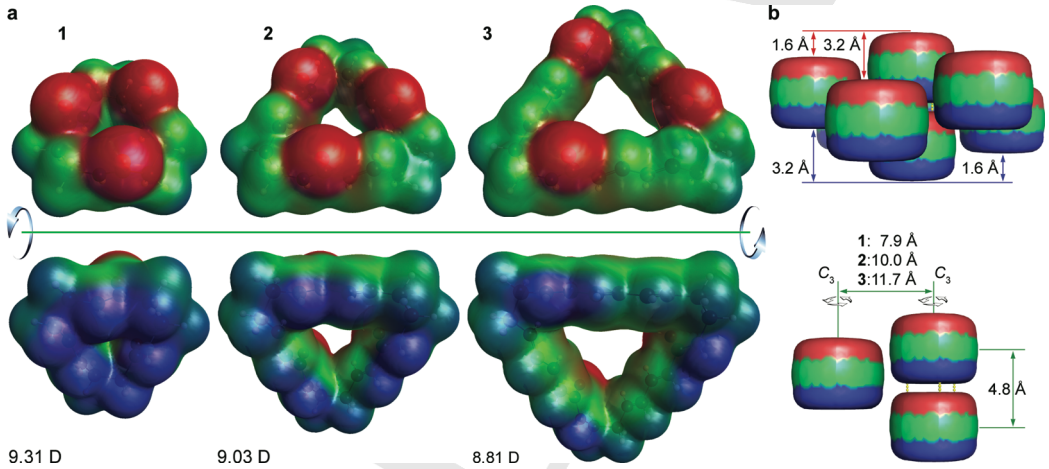

Figure 4. Electrostatic potentials maps and relative positions of rings 1-3 in their crystals. a. Electrostatic potentials displayed on 0.002 au isodensity surfaces of rings **1**-**3**. The maximum values (darkest blue) correspond to 0.050 au. The top views are seen from the δ-negative face where the carbonyl oxygen atoms stand, while the bottom views are seen from the δ-positive face where the NH amide groups are located. The strong polarization of the molecules is also supported by their calculated dipoles (DFT). **b**. All polar molecules **1**-**3** (red, green and blue colors are for δ–, neutral and δ+ regions respectively) adopt exactly the same relative spatial geometry. The middle reference column shows the three H-bonds between all pairs of polar macrocycles within the same stacks. The six satellite rings, belonging to neighbouring stacks, are shifted along the polar axis, such that all polar regions, within the crystal, sit next to oppositely charged or neutral regions.

Each nanotube is surrounded by six parallel nanotubes placed at the six corners of a hexagon (the distances between axes of adjacent nanotubes are 7.93 Å, 9.99 Å, and 11.74 Å for **1**, **2** and **3** respectively). These peripheral nanotubes can be divided into two families classified according to the translation they undergo along the c axis. The first family comprises the nanotubes placed at the arbitrary angles 0°, 120° and 240° and which are offset by 1.60 Å, according to c, with respect to the central reference nanotube. For the second family, the nanotubes placed at the angles of 60°, 180° and 300° are offset by -1.60 Å. It is thus observed that there are in fact three families of nanotubes in each crystal, which are simply offset from one another. [5,19,45] Consequently, no macrolactam is perfectly opposite to another directly adjacent in the a-b plane of the crystal. It is understood that this would be unfavorable since it corresponds to a destabilizing Keesom interaction. [28] Of course, Keesom interactions, whether stabilizing or not, can quickly become insignificant compared to other non-covalent stronger interactions. However, it seems clear in these cases that they have been able to act in synergy with other weak bonds.

In order to better understand the distribution of the partial charges of each monomer, their electrostatic potential maps were calculated (DFT). [29,47] It appears that the poles carry opposite charges, while the equator is neutral (Fig. 4a). Each molecule can be naively described as the sandwich of a neutral slice between two slices of opposite charges. All these observations lead to a plausible and simple explanation of this surprising crystalline arrangement. Each charged region is surrounded by six lateral direct neighbors and one oppositely charged neighbor directly bound by three hydrogen bridges within the same nanotube (Fig. 4b). This latter neighbor exerts a much greater influence than the lateral neighbors. However, due to the shifting of the nanotubes

relative to each other, [5] three oppositely charged neighboring regions (positions 0°, 120° and 240° of the hexagon already described) stabilize the lattice by favorable electrostatic interactions. The three remaining regions (60°, 180° and 300°), being neutral, do not really have any effect, except for the van der Waals interactions. Overall, the 3D crystal lattice, with all the parallel nanotubes, perfectly fulfills all the possibilities of weak bonds in terms of hydrogen bridges, electrostatic, dipole-dipole and van der Waals interactions.

This work might open the door to the rational design of organic ferroelectric crystals of a new kind, based on the alignment of macrolactams with very strong permanent dipoles. The threefold symmetry of these macrolactams, whose carbonyl function is conjugated with alkenes, imposes rigidity on the system and perfectly controls the orientation of the dipoles. This particular and unique geometry makes it possible to enlarge even further the size of macrocycles and channels simply by adding alkenes.

Acknowledgements

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Keywords: Macrolactam • Supramolecular nanotube • Dipole • Porous crystals • Hydrogen bonds

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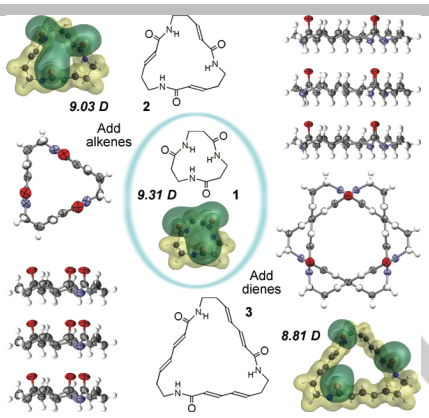
Very polar and rigid macrolactams **2** (9.03 D) and **3** (8.81 D), obtained by adding three alkenes and three dienes respectively to cyclotri-β-alanyl **1** (9.31 D) aggregate as “endless” stacks through backbone-backbone H-bond interactions and van der Waals contacts. All three triangular lactams crystallize in the trigonal system, all tubular macrodipoles being oriented in the same direction. Moreover, **3** forms channels capable of hosting guests.



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