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The missing link in the homologous series of lactams: the X-ray structure of valerolactam

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Abstract

Lactams are an important class of heterocyclic compounds and are widely used for industrial and pharmaceutical purposes. Even decades after initial lactam syntheses, research on their physical and chemical properties is still rewarding. It delivers valuable information on the reactivity of lactams and their conformational behavior. For the small and medium-sized parent lactams the X-ray structures have been well known, except for the 'missing link' the 6-membered valerolactam. An X-ray structure of valerolactam is described here for the first time stimulating a comparative discussion of the homologous lactam series. The experimental solid state conformation of valerolactam differs significantly from the calculated and energy-minimized ones reported in the literature. The amide bond length in valerolactam is more or less equal to other lactams. A comparison with the structure of cyclohexene revealed striking similarities arising from the partial C-N double bond in valerolactam caused by amide resonance.

INTRODUCTION

Lactams, *i.e.* cyclic amides, are an important class of heterocyclic compounds. By means of nomenclature they are sometimes considered as oxo derivatives of the respective cyclic amines. More common are their trivial names derived from the root of the respective carboxylic acid, *e.g.* the lactam containing seven carbon atoms is named enantholactam after enanthic acid (=heptanoic acid) (Figure 1). One of the oldest and best described lactams is the 7-membered cycle, *i.e.* caprolactam, caprolactam, which was described in the 19th century.[1] Additional members of the homologous series gained more and more significance.

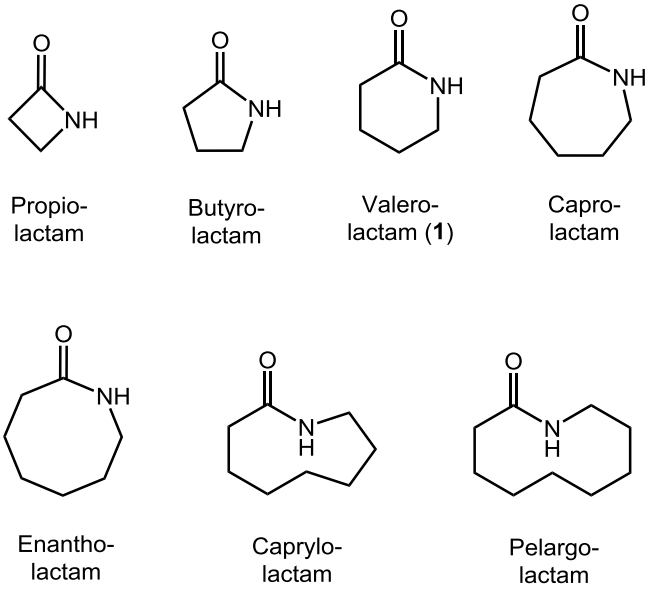


Figure 1. Nomenclature of small and medium-sized lactams (trivial names).

Lactams and their derivatives are widely used in industry,[2,3] occur in natural products chemistry,[4] and are employed as active pharmaceutical ingredients (APIs) with the β-lactam antibiotics as the most prominent examples.[5] Insight into their reactivity, thermodynamic and kinetic stability as well as their conformational behavior has provided crucial knowledge for biology and materials science based applications. As observed for non-cyclic amides, lactams possess a resonance stabilized C-N bond with partial double bond character, which goes in hand with resonance stabilization. For butyro-, valero- and enantholactam it was reported that the C-N double bond character is very similar resulting in comparable stability towards hydrolysis.[6] Another typical property of lactams is the existence of *cis* and *trans* forms resulting from different dihedral angles of the amide bond.[7,8]

During our studies on bridged lactams[9] we became interested in the conformation and solid state behavior of small and medium-sized lactams. For the underivatized lactams with ring sizes 4-10 the X-ray structures have been well known, except for the 'missing link' the 6-membered valerolactam (**1**). Valerolactam has been suggested as a system to mimic the base pairing in nucleic acids.[10] Moreover, **1** is a valuable precursor for the total synthesis of different natural products[11-14] and is frequently employed in the development of chemical methodologies.[15-17] Additionally, several bioactive compounds are valerolactam derivatives.[18-22] Only recently, the biotechnological production of valerolactam (**1**)[23] and a lactam biosensor[24] have been introduced. So far, the molecular structure of **1** has only been described in respective co-crystals[25-31] and metal complexes.[32-36] Here, we describe for the first time a crystal structure

of valerolactam (**1**) in the absence of other ligands, completing a homologous structural series of small and medium-sized lactams.

After some difficulties we were able to determine the molecular structure of **1** from commercially available valerolactam. Although the purchased compound exhibits seemingly well-formed crystals, the determination of its X-ray structure proved rather difficult due to apparent hygroscopicity combined with the low melting point of the substance (38-40 °C).[37] When taken out of the bottle, the crystals very quickly were dissolved (Figure 2) and gave only unsatisfying data (**1a** in ESI). In order to cool the crystals and prevent interaction with humidity we used a handmade cooling set-up (Figure S1, ESI), which finally facilitated the selection, measurement and structure determination of **1** (Table S1, ESI).

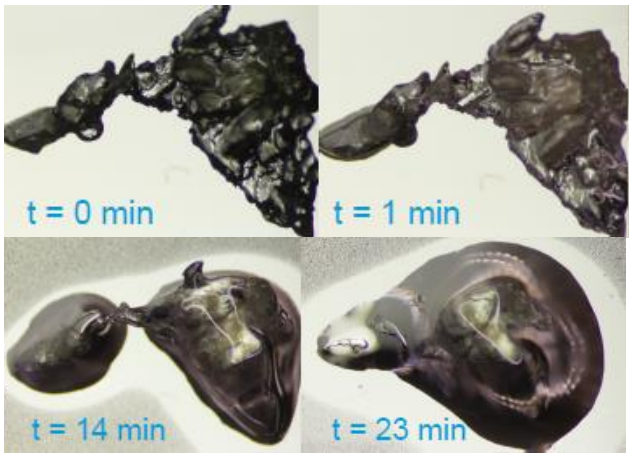
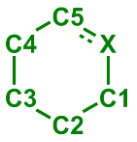
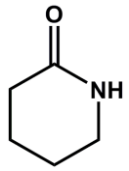
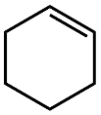
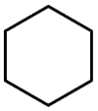
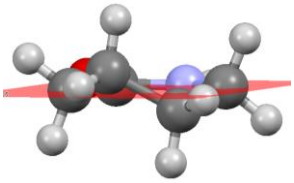
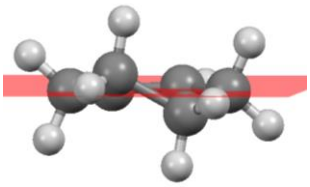


Figure 2. Images of valerolactam (**1**) exposed to air at room temperature on a microscope taken at different times.

Valerolactam (**1**) crystallizes in the monoclinic space group $P2_1/c$ with one molecule in the asymmetric unit or triclinic space group *P*-1 (**1a** in ESI, Figure S2). In **1**, the C-C bond lengths range from 1.5108(16) to 1.5225(16) Å. (The estimated standard deviations, esds, are given in brackets.) The experimental length of the amide bond [1.3344(16) Å] is somewhat shorter than the calculated one (1.372 Å).[38] The valerolactam molecule in co-crystals and crystalline metal complexes were found to have a somewhat shorter amide bond (Table S2 and S3, ESI). The amide region of valerolactam can be considered as planar [3.21(19)°], which differs considerably from the calculated values (MNDO calculations[39]: 20.4°; *ab initio* MO calculations[40]: -17.8 °). While additional conformations were found in the gas phase,[41] in the X-ray structure valerolactam features a half-chair conformation similar to those found in the respective cycloalkene, *viz.* cyclohexene.[42] The valerolactam atoms C2 and C3 deviate by 0.417(2) Å and 0.325(2) Å, respectively, from the C1-N1-C5-C4 mean plane; the equivalent atoms in cyclohexene deviate by 0.366 Å and 0.373 Å (Table 1). In valerolactam co-crystals the title compound develops quite variable torsion angles, though in most cases still half-chair conformations are adopted (Table S2, ESI). By way of interest, in metal complexes containing multiple valerolactam molecules bond lengths and torsions differ over a broad range as exemplarily shown for octakis(δ-valerolactam-O)-neodymium triperchlorate[43] (VOTKUK) (Table S3, ESI).

Table 1. Conformational parameters [°] of valerolactam (**1**), cyclohexene[a, 42] and cyclohexane.[b, 44]

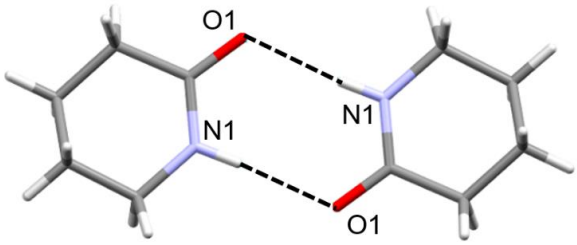
				
C1-C2-C3-C4	-61.06(14)	-61.2	-55.6
C2-C3-C4-C5	44.45(15)	44.9	55.1
C3-C4-C5-X	-15.84(16)	-13.9	-54.5
C4-C5-X-C1	3.21(19)	-2.05	55.6
C5-X-C1-C2	-19.81(18)	-13.6	-55.1
X-C1-C2-C3	48.21(15)	44.3	54.5
			---
C2/C3 deviation C4-C5-X-C1 mean plane [Å]	0.325(2), 0.417(2)	0.366, 0.373	---

[a] The crystal structure contains two molecules; we refer to the non-disordered one.
[b] The conformation for cyclohexane polymorph II at 115 K is shown.

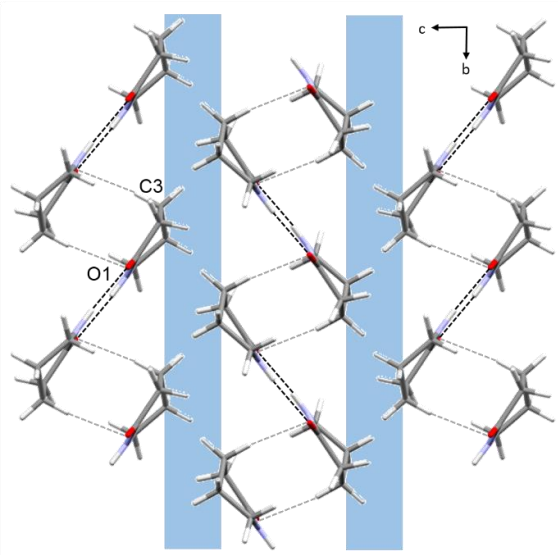
In the packing of **1** two lactam molecules are connected via strong N-H···O hydrogen bonds [d(N···O)=2.9070(14) Å] and form $R_2^2(8)$ amide dimers (Figure 3a). Double hydrogen-bonded valerolactam dimers have already been describe in solution.[Error! Bookmark not defined.] In the overall packing, the dimeric aggregates are interconnected via hydrophobic interactions and C-H···O contacts [d(C···O)=3.4210(17) Å] (Table 2) between C3 and the amide carbonyl; an $R_2^2(10)$ graph-set descriptor has been found (Figure 3b).

Table 2. Distances and angles of hydrogen bond type interactions in the molecular structure of valerolactam (**1**)

atoms	symmetry	distances [Å]		angle [°]
		D···A	H···A	D–H···A
1				
N(1)-H(1N)···O(1)	*-x*, *-y*, *-z*+1	2.9070(14)	2.057(18)	176.3(15)
C(3)-H(3B)···O(1)	*-x*, *-y*+1, *-z*+1	3.4210(17)	2.58	142.4



(a)



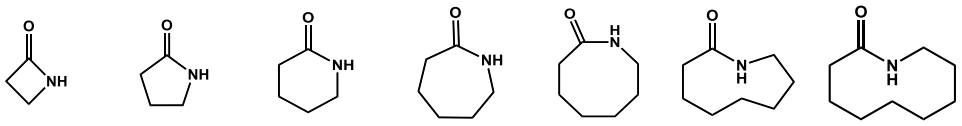
(b)

Figure 3. Molecular structure of valerolactam (**1**) (a) and its packing behavior (b). Hydrogen bonds (black) and C-H···O contacts (grey) are displayed as broken lines. Hydrophobic interactions are shaded.

So far, the X-ray structures of propio- (FEPNAP),[45] butyro- (NILYAI),[46] capro- (CAPLAC),[47] enantho- (ENANOL),[48] caprylo- (CAPRYL)[49] and pelargolactam (PELARG)[50] have been determined. In the following, we discuss the structure of the newly studied valerolactam in context of those of the other lactams, especially as it is a "missing link" between them.

For design of new non-β-lactam lactamase inhibitors,[51] it is important to know if during the hydrolysis of lactams the ring strain or the high carbonyl reactivity is rate-limiting. Imming and co-workers studied the hydrolysis of several lactams and found that the propio- and valerolactam are specifically labile in comparison to the others.[52] They postulated that not the C-N bond fission, but the formation of the tetrahedral intermediate was rate-determining. This hypothesis is underpinned by the fact that for the 4- to 9-membered lactams the length of the amide bonds are more or less equal for the whole series (1.328-1.335 Å) (Table 3, Figure 4). (The different temperatures during structure determination are clearly a source of uncertainty.) By way of interest, for the 10-membered ring (pelargolactam), the amide bond is considerably longer (1.426 Å). To the best of our knowledge X-ray structures of higher lactams have not been determined yet.

Table 3. Conformational and bonding parameters in the discussed series of lactams



Compound (CSD codes)	FEPNAP	NILYAI	**1**	CAPLAC	ENANOL	CAPRYL	PELARG
T [K]	170	173	173	295	98	295	295
d[C(O)-NH] [Å]	1.333(2)	1.335(2)	1.3344(16)	1.328(2-3)	1.334(2)	1.334(3-4)	1.426[a]
Hydrolysis kinetics[52] k_2 [M^{-1} s^{-1}]	$2.37\cdot10^{-4}$	$5.59\cdot10^{-6}$	$1.21\cdot10^{-4}$	$3.21\cdot10^{-6}$	$1.36\cdot10^{-7}$	$2.72\cdot10^{-7}$	-[b]
C-C(O)-NH-C dihedral angle [°]	0.0(2) (*cis*)	4.3(1) (*cis*)	3.21(19) (*cis*)	-4.2(4) (*cis*)	1.4(3) (*cis*)	148.4(5) (*trans*)	167.1[a] (*trans*)
H bonding pattern	$R_2^2(8)$ amide dimers + C(4) amide chains	$R_2^2(8)$ amide dimers	$R_2^2(8)$ amide dimer	$R_2^2(8)$ amide dimer	C(4) amide chains	C(4) amide chains	C(4) amide chains
KPI[c] [%]	74.8	71.8	69.2	67.4	70.7	69.3	-[d]
d(H···A)	2.19	1.98	2.057(18)	1.84	1.94	2.03	-[d]
d(D-H···A)	2.967	2.921	2.9070(14)	2.895	2.815	2.864	2.758
<(DHA)	152.8	172.4	176.3(15)	172.7	172.8	165.2	-[d]

[a] no esd given
[b] not determined in reference[52]
[c] Kitaigorodskii packing index
[d] not determined as the X-ray structure has only been resolved incompletely.

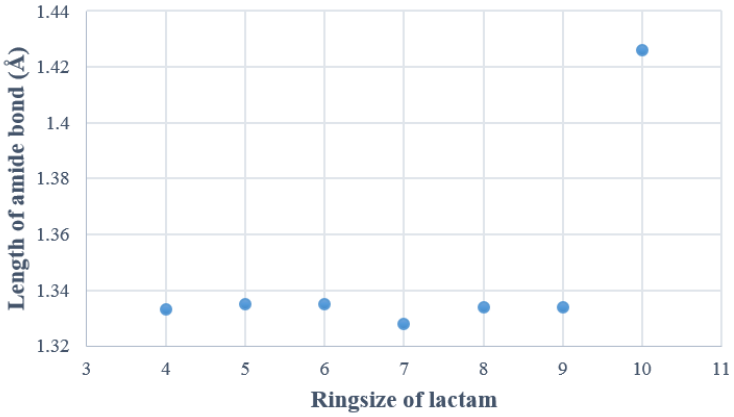


Figure 4. Diagram of the amide bond lengths in connection with the lactam ring size. (The data for the pelargolactam, ring size=10, should be interpreted cautiously due to the incomplete crystallographic data for this particular compound.)

As expected, all lactams compared here are engaged in strong N-H···O hydrogen bonds. Though, depending on the ring size, two different graph-set descriptors are observed. For 5- to 7-membered lactams, cyclic $R_2^2(8)$ interactions are preferred. For 8- to 10-membered lactams,

C(4) chains can be found. The 4-membered propiolactam displays both, N-H···O rings and chains, leading to the highest Kitaigorodskii packing index (KPI) (74.8 %) observed in this series.

Figure 5 shows the distance of hydrogen bond donors (D) and acceptors (A) with respect to the lactam ring size. By way of interest, for lactams up to caprolactam the D···A distances between the $R_2^2(8)$ dimers decrease (2.97 to 2.90 Å). In the 8-membered enantholactam displaying C(4) chains instead dimers, we found the shortest N-H···O distance (2.815 Å) for all of the unsubstituted lactams. For larger rings the respective distances in the N-H···O chains are increasing again, which may be connected with the switch from *cis* to *trans* amides in caprylo- and pelargolactam (Figure S3, ESI). Despite the varying D···A distances in the N-H···O hydrogen bonds, the DHA angles only differ slightly (165.2-176.3 °) except for the 4-membered lactam (120.0 °; 152.8 °); this can be explained with the small ring size of propiolactam (Figure S4, ESI). Interestingly, α-chlorovalerolactam[53] (CSD code: CLVALA) has a slightly longer amide bond than the parent compound **1** (1.365 Å) and develops C(4) chains [d(N···O)=2.910 Å] as observed for enantholactam.

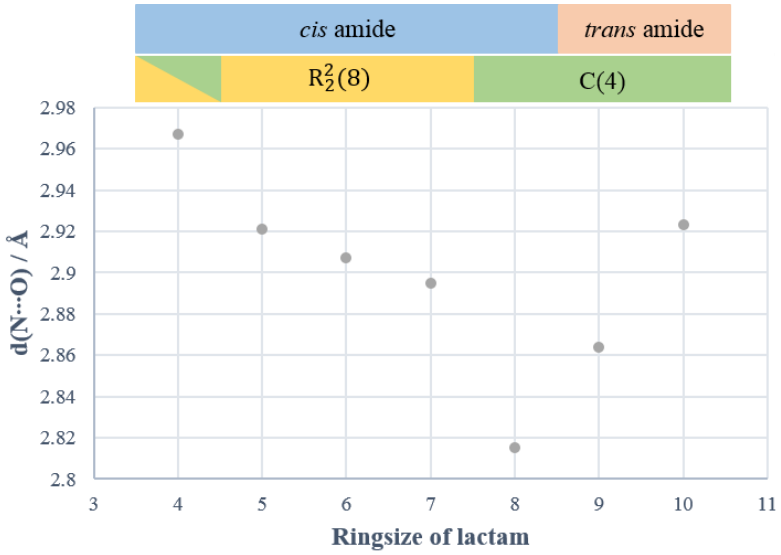


Figure 5. H bonding donor···acceptor distances in the molecular structures with reference to the lactam ring size (4-10).

In conclusion, we described for the first time the X-ray structure of valerolactam, which stimulated a comparative discussion of the homologous series of lactams. Surprisingly, the amide bond length in the title compound is more or less equal to other lactams, hence, the different ring strains have only a minor influence on the amide length. As the kinetics for the hydrolysis of lactams differ for the individual lactams, the rate of lactam hydrolysis is determined by the formation of the tetrahedral intermediate not by the C-N bond fission. The experimental conformation of valerolactam in the solid state differ significantly from the calculated and energy-minimized ones reported in the literature. A comparison with the structure of cyclohexene revealed striking similarities arising from the partially C-N double bond in valerolactam. It would be interesting to see if this can also be translated to derivatives of valerolactam and cyclohexene.

EXPERIMENTAL SECTION

Suitable crystals of **1** and **1a** (ESI) were selected directly from a purchased bottle of valerolactam (Fluorochem). Single crystal X-ray diffraction was performed at 173 K with a Bruker D8 Venture diffractometer using a Cu-K_α source. Structure solution was carried out with shelxs[54] and structure refinement with shelxl[54] was finished using ShelXle[55] software. The crystallographic data for the structures of **1** and **1a** have been deposited with the Cambridge Crystallographic Data Centre; CCDC number: 1839815 (**1**), 1839822 (**1a**).

ASSOCIATED CONTENT

Supporting Information

Selected details of the data collection and additional figures underlining the structure description. The Supporting Information is available free of charge on the xxx website at DOI: xxx

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Notes

The authors declare no competing financial interest.

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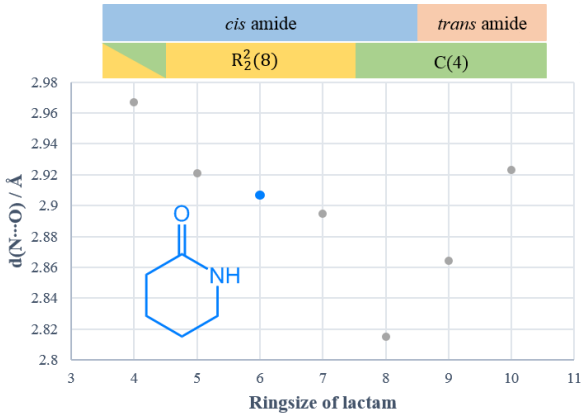
The missing link in the homologous series of lactams: the X-ray structure of valerolactam

Christian Weck, Elisa Nauha, Tobias Gruber



For the small and medium-sized parent lactams the X-ray structures are well known for many years – except for the 'missing link' valerolactam, *i.e.* the 6-membered lactam. Its X-ray structure is described here for the first time stimulating a comparative discussion of the homologous series of lactams.