Distinct molecular structures and hydrogen bond patterns of α,α -diethyl-substituted cyclic imide, lactam, and acetamide derivatives in crystalline phase

Arcadius V. Krivoshein^{1,*}, Carlos Ordonez², Victor N. Khrustalev^{3,4}, and Tatiana V. Timofeeva^{3,*}

¹ Department of Basic and Social Sciences, Albany College of Pharmacy and Health Sciences, 106 New Scotland Avenue, Albany, NY 12208, United States

² MS Program in Applied Chemistry and ³ Department of Biology and Chemistry, New Mexico Highlands University, Box 9000, Las Vegas, NM 87701, United States

⁴ Department of Inorganic Chemistry, Peoples' Friendship University of Russia, 6 Miklukho-Maklaya Street, Moscow, 117198, Russian Federation

* to whom correspondence should be addressed at arcadius.krivoshein@acphs.edu (A. V. K.) or vtimofeeva@nmhu.edu (T. V. T.)

ABSTRACT

α,α -Dialkyl- and α -alkyl- α -aryl-substituted cyclic imides, lactams, and acetamides show promising anticonvulsant, anxiolytic, and anesthetic activities. While a number of crystal structures of various α -substituted cyclic imides, lactams, and acetamides were reported, no in-depth comparison of crystal structures and solid-state properties of structurally matched compounds have been carried out so far. In this paper, we report molecular structure and intermolecular interactions of three α,α -diethyl-substituted compounds - 3,3-diethylpyrrolidine-2,5-dione, 3,3-diethylpyrrolidin-2-one, and 2,2-diethylacetamide - in the crystalline phase, as studied using single-crystal X-ray diffraction and IR spectroscopy. We found considerable differences in the patterns of H-bonding and packing of the molecules in crystals. These differences correlate with the compounds' melting points and are of significance to physical pharmacy and formulation development of neuroactive drugs.

KEYWORDS: cyclic imides, lactams, acetamides, antiepileptic, X-ray diffraction, IR spectroscopy

GRAPHICAL ABSTRACT

1. Introduction

α,α -Dialkyl- and α -alkyl- α -aryl-substituted cyclic imides, lactams, and acetamides show promising pharmacological (*e.g.*, anticonvulsant, anxiolytic, and anesthetic) activities. α -Substituted cyclic imides (succinimides in particular) are well established as antiepileptic drugs. For instance, methsuximide (1,3-dimethyl-3-phenylpyrrolidine-2,5-dione) is a broad-spectrum anticonvulsant valuable in treatment of medically refractory (*i.e.*, drug-resistant) epilepsy [1]. Ethosuximide (3-ethyl-3-methylpyrrolidine-2,5-dione) is the drug of choice in the treatment of absence seizures [2]. α -Substituted lactams (*e.g.*, 3,3-diethylpyrrolidin-2-one) are promising experimental anticonvulsants with good safety margin [3,4]. α -Substituted acetamides also show promising antiepileptic activity. For example, Bialer and Yagen with collaborators synthesized a number of α -alkyl-substituted acetamides and tested their anticonvulsant activity, metabolism, and pharmacokinetics in animals [5-7]. Some α -substituted acetamides, lactams, and cyclic imides (methsuximide, ethosuximide, valnoctamide) are used clinically, and a few others are undergoing clinical trials. Better understanding of solid-state chemistry of these structurally related drugs is expected to help modulate their pharmaceutically relevant properties (*e.g.*, solubility, bioavailability, and stability upon storage).

While the solid-state chemistry of α -substituted succinimides has been studied extensively (including two recent studies from our groups [8,9]), the same cannot be said about α -substituted lactams and acetamides. To the best of our knowledge, only two crystal structures of α -substituted lactams have been solved: one for 1,3-dioxole-2-spiro-4'-(3',3'-diethylpyrrolidin-2'-one) [10] and another for 3-allyl-3-phenylpiperidin-2-one [11] (the latter paper concerns organic

synthesis, and no discussion of the crystal structure of 3-allyl-3-phenylpiperidin-2-one was given). Regarding α -substituted acetamides, crystal structures of several alkyl-substituted acetamide derivatives have been reported [12-14], including our groups' recent report concerning crystal structures and absolute configurations of enantiomers of 2-phenylbutyramide [8].

Thus, while a number of crystal structures of various α -substituted cyclic imides, lactams, and acetamides were reported, no in-depth comparison of crystal structures and solid-state properties of structurally matched compounds have been carried out so far. We present such a comparison here. To avoid possible uncertainties due to chiral factors, achiral α,α -dialkyl derivatives of pyrrolidine-2,5-dione (succinimide), pyrrolidin-2-one (γ -butyrolactam), and acetamide were used (Figure 1).

Figure 1. Structures of the compounds under investigation

2. Materials and methods

2. 1. *Compounds*

3,3-Diethylpyrrolidine-2,5-dione and 3,3-diethylpyrrolidin-2-one were purchased from Enamine Ltd. (Cincinnati, OH). 2,2-Diethylacetamide (2-ethylbutyramide) was custom-synthesized for us, also by Enamine Ltd. Hexanes, acetone, and acetonitrile (HPLC grade or ACS grade) were purchased from EMD Millipore (Billerica, MA).

2. 2. *Crystallization*

Typically, crystals were grown by slow evaporation of 15 mg/ml solutions of the compounds under investigation in hexanes/acetone (2:1) in glass test tubes at room temperature in a desiccator. In some experiments, crystals were grown by slow evaporation of 40 mg/ml solutions of the compounds under investigation in acetonitrile/water (1:1) in glass test tubes at room temperature in desiccator.

2. 3. *Single-crystal X-ray diffraction analysis*

The data were collected at 100 K or 200 K on a Bruker-AXS SMART APEX II CCD diffractometer using graphite-monochromatized MoK α radiation ($\lambda = 0.7107 \text{ \AA}$) and corrected for absorption using the *SADABS* program [15]. Crystals were mounted on a needle and cooled in a stream of N₂ vapor. The crystal structures were solved by direct methods and refined by a full-matrix least squares technique on F^2 with anisotropic displacement parameters for non-

hydrogen atoms. The hydrogen atoms at nitrogens were objectively localized in the difference Fourier maps and refined with fixed isotropic displacement parameters: $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{N})$. The hydrogen atoms at carbons were placed in calculated positions and included into the refinement within the riding model with fixed isotropic displacement parameters: $U_{\text{iso}}(\text{H}) = 1.5U_{\text{eq}}(\text{C})$ for CH_3 groups and $1.2U_{\text{eq}}(\text{C})$ for the other groups. All calculations were carried out using the *SHELXTL* program [16]. Crystallographic data for compounds **1-3** have been deposited with the Cambridge Crystallographic Data Center. CCDC 1419201 (**1**), CCDC 1419202 (**2**), and CCDC 1419203 (**3**) entries contain supplementary crystallographic data for this paper. These data can be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or www.ccdc.cam.ac.uk).

2. 4. *Infrared (IR) spectroscopy*

Infrared spectra of finely ground crystals were recorded at room temperature (20–22 °C) on Nicolet iS10 FT-IR spectrometer fitted with Smart iTR single-reflection ZnSe ATR accessory (Thermo Scientific, Waltham, MA). The spectral range was 4000 to 650 cm^{-1} , and the resolution was set at 2 cm^{-1} . Thirty-two spectra were collected and averaged for each sample, and sixty-four spectra – for each background (with the automatic atmospheric suppression enabled). Omnic ver. 8.3.103 software (Thermo Scientific, Waltham, MA) was used to record the spectra and apply Advanced ATR Correction and linear baseline correction.

2. 5. Melting point determination

Melting curves were recorded in the OptiMelt MPA100 automated melting point system with digital image processing technology controlled by MeltView ver. 1.107 software (Stanford Research Systems, Sunnyvale, CA). A heating rate of 1 °C / min was used. Since the instrument was factory calibrated at that heating rate, our reported melting points (defined as clear points, 10% threshold) can be regarded as the true, thermodynamic melting points.

Melting points were predicted using a model based on electrotopological state (E-state) formalism [17] as implemented in the OCHEM Online Chemical Modeling Environment [18].

3. Results

3.1. Molecular structures

Panels A, B, and C in Figure 2 show the molecular structures of 3,3-diethylpyrrolidine-2,5-dione **1**, 3,3-diethylpyrrolidin-2-one **2**, and 2,2-diethylacetamide **3** determined by single-crystal X-ray diffraction at 100 K (with the crystallographic data given in Table 1). Although there is a considerable degree of overall structural similarity, some differences are evident. For example, the conformations of the ethyl substituents differ significantly. In cyclic imide **1**, both of the ethyl groups have *gauche* orientation relative to the C(2)-C(7) and C(2)-C(5) bonds. In lactam **2** and acetamide **3**, on the other hand, only one of the ethyl groups is in *gauche* orientation relative to the C(2)-C(5) bond, with the second ethyl substituents being in *anti* orientation relative to the C(2)-C(7) bond in lactam **2** and the C(2)-C(3) bond in acetamide **3**. The superimposed molecular structures of these three compounds (Figure 2D) clearly demonstrate the similarity of the CO-NH fragment and dissimilarity of the ethyl substituents' orientation, with the numerical values of the corresponding torsion angles given in Table 2. For the two cyclic compounds, there are also slight differences in the geometry of the five-member ring: while in cyclic imide **1**, the ring is almost planar (mean deviation from the planarity is 0.0252 Å), in lactam **2**, the presence of two neighboring sp^3 atoms, C(3) and C(4), results in a more pronounced (0.0708 Å) mean deviation from the planarity.

In acetamide **3**, C(4) and C(6) atoms are disordered. During the refinement process, the occupancies of these atomic positions were allowed to vary, giving two alternative positions for the C(4) atom (occupancies 0.46 and 0.54) and two alternative positions for the C(6) atom

(occupancies 0.42 and 0.58). The corresponding values of torsion angles are listed in Table 2.

These data demonstrate conformational flexibility of the ethyl substituents due to crystal packing forces and suggest that the same or even greater flexibility may be observed in aqueous solutions in physiological conditions.

Figure 2. ORTEP diagrams of 3,3-diethylpyrrolidine-2,5-dione **1** (panel A), 3,3-diethylpyrrolidin-2-one **2** (panel B), and 2,2-diethylacetamide **3** (panel C). The superimposed structures (with hydrogen atoms omitted) of 3,3-diethylpyrrolidine-2,5-dione **1** (solid lines), 3,3-diethylpyrrolidin-2-one **2** (dashed lines), and 2,2-diethylacetamide **3** (hollow lines) are shown in panel D.

Table 1

Crystallographic data for the compounds under investigation

Parameter	Compound		
	Cyclic imide 1	Lactam 2	Acetamide 3
Empirical formula	C ₈ H ₁₃ NO ₂	C ₈ H ₁₅ NO	C ₆ H ₁₃ NO
Formula weight	155.19	141.21	115.17
<i>T</i> , K	100	100	100
Radiation (λ), Å	0.71073	0.71073	0.71073
Crystal size, mm	0.15×0.16×0.50	0.05×0.24×0.25	0.12×0.17×0.22
Crystal system	monoclinic	triclinic	monoclinic
Space group	P2 ₁ /c	P-1	P2 ₁ /c
<i>a</i> , Å	5.980(1)	6.261(3)	10.813(2)
<i>b</i> , Å	10.655(2)	6.364(3)	7.353(1)
<i>c</i> , Å	13.135(3)	10.976(6)	9.410(1)
α , deg.	90	77.415(8)	90
β , deg.	93.692(3)	88.637(8)	101.425(2)
γ , deg.	90	75.051(8)	90
<i>V</i> , Å ³	835.3(3)	412.1(4)	733.3(2)
<i>Z</i>	4	2	4
<i>d</i> _c , g/cm ³	1.234	1.138	1.043
μ , mm ⁻¹	0.088	0.074	0.070
2 θ_{max} , deg.	56.0	50.5	56.0
Reflections collected	7563	1473	6648
Unique reflections	1976	1176	1768
<i>R</i> _{int}	0.025	0.010	0.023
Reflections with $I > 2\sigma(I)$	1849	937	1625
Refined variables	100	91	92
$R(F^2 > 2\sigma(F^2))$	0.0365	0.0579	0.0408
Goodness-of-fit on F^2	1.072	1.042	0.953
$wR(F^2)$, all data	0.1003	0.1624	0.1217

Table 2

Torsion angles between the C=O group adjacent to α carbon and the ethyl substituents

Compound	Torsion angle (deg)	
	First ethyl substituent	Second ethyl substituent
Cyclic imide 1	-54.95(11) C(1)-C(2)-C(5)-C(6)	58.75(10) C(1)-C(2)-C(7)-C(8)
Lactam 2	-56.9(2) C(1)-C(2)-C(5)-C(6)	-179.4(2) C(1)-C(2)-C(7)-C(8)
Acetamide 3 *	-160.2(6)	60.4(6)
	-173.5(6)	60.2(4)
	C(1)-C(2)-C(3)-C(4)	C(1)-C(2)-C(5)-C(6)

* for each torsion angle, two values corresponding to disordered positions of atoms C(4) and C(6) are given

3.2. Crystal packing

Figure 3 illustrates packing of the molecules of the compounds under investigation in the crystalline phase. Since no substantial differences were observed between crystals grown from hexanes/acetone (2:1) and acetonitrile / water (1:1), only data obtained with crystals grown from hexanes/acetone are discussed.

The existence of both electron acceptor (carbonyl) and electron donor (amino) groups in these compounds (Figure 1) enables the formation of intermolecular H-bonds. Indeed, X-ray diffraction crystallography data for cyclic imide **1** and lactam **2** demonstrate the existence of a single symmetrically independent H-bond (Table 3) that allows for formation of similar centrosymmetric molecular dimers in both compounds (it should be noted that in cyclic imide **1**,

only one of the two carbonyls is involved in H-bonding). While the packing patterns of compounds **1** and **2** are different (Figures 3A and 3B; Table 1), unit cell parameters and volumes show some similarity (especially considering that the unit cell volume of cyclic imide **1** is twice that of lactam **2**).

Table 3

Intermolecular hydrogen bonds (Å and deg.) in the crystal structures of the compounds under investigation

Compound	D - H...A	d(D - H)	d(H...A)	d(D...A)	∠(D - H...A)
Cyclic imide 1	N(1) – H(1A)...O(1) ¹	0.86	2.00	2.847(1)	167.6
Lactam 2	N(1) – H(1A)...O(1) ²	0.86	2.07	2.902(3)	161.6
Acetamide 3	N(1) – H(1A)...O(1) ³	0.86	2.16	3.017(1)	173.0
	N(1) – H(1B)...O(1) ⁴	0.86	2.06	2.901(1)	165.9

D – proton donor;

A – proton acceptor.

Symmetry transformations used to generate equivalent atoms: ¹ -x+1, -y, -z+1; ² -x+1, -y+2, -z; ³ -x, -y, -z+1; ⁴ x, -y+1/2, z-1/2.

Acetamide **3** had been previously crystallized from ethanol, and its structure was determined at room temperature [13]; unfortunately, hydrogen atom positions were not determined in that study, making it impossible to characterize its H-bonding geometry. Therefore, we reinvestigated this compound (crystallized from hexanes/acetone) at 100 K. We found molecular layers formed *via* a two-dimensional system of hydrogen bonds located in the inner plane of the layer (Figure

3C). The ethyl groups are on the outside of the layers and may weakly interact with other layers through van der Waals forces.

Figure 3. Supramolecular synthons and crystal packing in 3,3-diethylpyrrolidine-2,5-dione **1** (panel A), 3,3-diethylpyrrolidin-2-one **2** (panel B), and 2,2-diethylacetamide **3** (panel C).

3.3. IR spectra

The solid-state IR spectra of 3,3-diethylpyrrolidine-2,5-dione **1**, 3,3-diethylpyrrolidin-2-one **2**, and 2,2-diethylacetamide **3** were recorded using ATR sampling; the regions corresponding to the C=O and N-H group frequencies are shown in Figure 4.

Figure 4. ATR IR spectra of 3,3-diethylpyrrolidine-2,5-dione **1**, 3,3-diethylpyrrolidin-2-one **2**, and 2,2-diethylacetamide **3**. The N-H stretch region is shown in panel A, and the C=O stretch region is shown in panel B. See Table 4 for peak frequencies and assignments.

The IR spectrum of 3,3-diethylpyrrolidine-2,5-dione **1** (Figure 4, red trace) is overall similar to that of 3-ethyl-3-methylpyrrolidine-2,5-dione in KBr pellets [19], 3-methyl-3-phenylpyrrolidine-2,5-dione (ATR sampling) [8], and 3-ethyl-3-phenylpiperidine-2,6-dione in KBr pellets [20].

The N-H (3185 cm^{-1}) and C=O (1675 cm^{-1}) stretching frequencies in the IR spectrum of 3,3-diethylpyrrolidin-2-one **2** (Figure 4, green trace) are very close to the values (3199 cm^{-1} and 1679 cm^{-1} , respectively) reported by Covey with collaborators [3] for thin films of this compound on an NaCl plate.

The IR spectrum of 2,2-diethylacetamide **3** (Figure 4, black trace) is very similar to its spectrum in KBr pellets reported by Jart [21]. It is also similar to IR spectra of homologous acetamides (acetamide, propionamide, butyramide, isobutyramide, isovaleramide, valpromide) [21,22].

For the compounds under investigation, the two most structurally informative IR spectral regions are the ones corresponding to stretching vibrations of N-H and C=O groups (Table 4).

Table 4

Vibrational modes of the compounds under investigation crystallized in the crystalline state

Vibrational mode	IR frequency, cm ⁻¹		
	Cyclic imide 1	Lactam 2	Acetamide 3
$\nu(\text{N-H})$	3176	3185	3342 (as), 3168 (s)
$\nu(\text{N-H})^*$	3060	3085	-
$\nu(\text{C=O})$	1697 (as), 1788 (s)	1675	1662
$\delta(\text{N-H})$	Not appl.	Not appl.	1627

as – asymmetric vibrations;

s – symmetric vibrations;

*Fermi resonance between the $\nu(\text{N-H})$ band and the $\nu(\text{C=O}) + \delta(\text{N-H})$ combination band.

The N-H stretching frequencies (Amide B/Imide B band) are very similar for cyclic imide **1** and lactam **2**. The slight (9 cm⁻¹) difference can be explained by the N-H bond being slightly stronger in **1** compared to **2** (Table 3). For both of the compounds, an additional lower-frequency

band due to Fermi resonance between the $\nu(\text{N-H})$ band and the $\nu(\text{C=O})+\delta(\text{N-H})$ combination band ($1445\text{-}1470\text{ cm}^{-1}$) was observed.

The N-H stretching frequencies of acetamide **3**, with both asymmetric (Amide A, 3342 cm^{-1}) and symmetric (Amide B, 3168 cm^{-1}) modes present, are substantially different from those of cyclic imide **1** and lactam **2**.

The frequency of the C=O stretch (Amide I/Imide I band) is similar for all three compounds ($1662\text{-}1697\text{ cm}^{-1}$, Table 5). For acetamide **3**, the N-H in-plane (“scissors”) bending frequency (Amide II band) was observed at 1627 cm^{-1} .

An additional, less intense band at 1778 cm^{-1} was observed in the IR spectrum of cyclic imide **1** (Figure 4B). The assignment of this band is somewhat debatable. Uno and Machida [23] suggested that this band in succinimide could be due to “free” (non-H-bonded) carbonyls. Since only one of the two carbonyls participates in the hydrogen bond (Figure 3A), this seemed quite feasible. However, later studies demonstrated that this band splitting is observed in both *N*-unsubstituted and *N*-substituted succinimides [24] and thus cannot originate from hydrogen bonding.

Thus, this additional band is likely to originate from vibrational coupling of the two carbonyl groups [25,26]: the higher-frequency (1778 cm^{-1}) band is due to symmetric (in-phase) stretching vibration, while the lower-frequency (1697 cm^{-1}) band is due to asymmetric (out-of-phase) stretching vibration.

3.4. Melting points

We measured the melting point of 3,3-diethylpyrrolidine-2,5-dione **1** as 84.0 °C (Table 5). No literature data are available for this compound. However, the melting points of 3-ethylpyrrolidine-2,5-dione and 3-ethyl-3-methylpyrrolidine-2,5-dione are in the 64 to 76 °C range [27,28]. Our value for the melting point of 3,3-diethylpyrrolidin-2-one **2** (53.5 °C; Table 5) is the same as the one (52-53 °C) determined by Covey and collaborators [3]. The melting point of 2,2-diethylacetamide **3** (112.9 °C; Table 5) is very close to the one (109.0-109.5 °C) determined by Jart [21].

Table 5

Bulk physicochemical properties of the compounds under investigation in the crystalline state

Compound	Number of intermolecular H-bonds ¹	Density (g/cm ³) ¹	Melting point (°C)	
			Exp ²	Calc ³
Cyclic imide 1	2	1.234	84.0 ± 0.4	94
Lactam 2	2	1.138	53.5 ± 0.2	47
Acetamide 3	4	1.043	112.9 ± 0.1	61

¹ from single-crystal X-ray diffraction data; ² experimental values (clear point), three to five independent measurements (M ± SD); ³ calculated using the OCHEM Predictor software (see Materials and Methods).

The predicted melting points for 3,3-diethylpyrrolidine-2,5-dione **1** and 3,3-diethylpyrrolidin-2-one **2** are in good agreement with experimentally obtained values (Table 5). However, for 2,2-diethylacetamide **3**, the predicted melting point is much lower than the actual value (Table 5). The discrepancy is likely due to the fundamentally different pattern of H-

bonding in acetamide **3** compared to cyclic amide **1** or lactam **2** (see above) and the software's inability to account for that.

4. Discussion

As we mentioned in the Introduction, the solid-state chemistry of α -substituted cyclic imides, lactams, and acetamides is of considerable interest to pharmaceuticals of neuroactive drugs. In order to facilitate the structural comparison of these classes of compounds, we chose to examine three α,α -diethyl-substituted, achiral derivatives: 3,3-diethylpyrrolidine-2,5-dione **1**, 3,3-diethylpyrrolidin-2-one **2**, and 2,2-diethylacetamide **3** (Figure 1). The question we asked in this study is “What are the structural differences between these model compounds in the crystalline phase?”

Our single-crystal X-ray diffraction experiments revealed substantial differences in crystal packing and in molecular conformation for the three compounds under investigation.

In the crystalline phase, 3,3-diethylpyrrolidine-2,5-dione **1** forms H-bound dimers. Using the graph set nomenclature of H-bond patterns proposed by Etter with collaborators [29], the supramolecular synthons of this compound are designated $R_2^2(8)$. Interestingly, we previously observed a very different molecular packing for another cyclic imide, 3-methyl-3-phenylpyrrolidine-2,5-dione [8]. In that case, dimer formation was not observed; instead, one-dimensional H-bonded chains were found. These differences are likely due to the different size and conformational flexibility of the substituents at the α position.

The molecular conformation and packing in 3,3-diethylpyrrolidin-2-one **2** are overall similar to those in 3,3-diethylpyrrolidine-2,5-dione **1** - the additional carbonyl group in the latter compound does not act as an H-bond acceptor. However, the conformations of ethyl substituents

at the α position are substantially different. A comparison of the geometric properties of hydrogen bonds (Table 3) indicated that that H-bonding is somewhat weaker in the dimers of lactam **2**. Interestingly, a 3,3-diethylpyrrolidin-2-one derivative with a dioxolane substituent in position 4 has a substantially different molecular packing while retaining the H-bonded dimer motif [10].

The extended H-bond network of 2,2-diethylacetamide **3**, a two-dimensional layer, can be described as $R_6^4(16)R_2^2(8)$. At the same time, the molecular packing of three structurally related α,α -disubstituted acetamides - 2-ethyl-5-methylhexanamide [14], 2-ethylpentanamide [14], and 2-phenylbutyramide [8] - is a one-dimensional ribbon.

The differences in the molecular structure and H-bonding are reflected in IR spectra (Figure 4; Table 4): for 3,3-diethylpyrrolidine-2,5-dione **1**, 3,3-diethylpyrrolidin-2-one **2**, and 2,2-diethylacetamide **3**, the lengths of the C=O bonds (for carbonyls involved in H-bonds) are $1.223 \text{ \AA} < 1.238 \text{ \AA} < 1.242 \text{ \AA}$, while the corresponding frequencies of the C=O stretch are $1697 \text{ cm}^{-1} > 1675 \text{ cm}^{-1} > 1662 \text{ cm}^{-1}$.

These structural differences are also reflected in the bulk physicochemical properties of the compounds under investigation (Table 5). For the $R_2^2(8)$ synthons of compounds **1** and **2**, the melting points are influenced by van der Waals forces and H-bonds. Thus, the melting point of the denser (1.234 g/cm^3) cyclic imide **1** is approximately 30 °C higher than that of the less dense (1.138 g/cm^3) lactam **2**. The thermal stability of the $R_6^4(16)R_2^2(8)$ synthon of acetamide **3** is greatly enhanced by the additional H-bonds, and van der Waals forces do not play any important role. Thus, the melting point of acetamide **3** is the highest of the three compounds (even though its density is the lowest).

Interestingly, the melting point of 2,2-diethylacetamide **3** (113 °C; Table 5) is in fact higher than the melting point of 2-phenylbutyramide (85 °C; Table 4 in [8]), despite the former being less dense (1.043 g/cm³) than the latter (1.160 g/cm³). Since these two compounds have the same H-bond pattern, the above differences in melting points suggest that the bulky phenyl groups decrease the thermal stability of crystalline lattices formed by acetamides.

The results presented in this paper are expected to help in developing a broadly applicable and predictive understanding of intermolecular interactions governing the formation of crystal lattices of cyclic imides, lactams, and acetamides. Such a predictive understanding will hopefully be of value to the physical pharmacy and formulation development of neuroactive drugs.

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