Journal of Molecular Structure 1121 (2016) 196–202

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: http://www.elsevier.com/locate/molstruc

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

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ARTICLE INFO

Article history:
Received 14 March 2016
Accepted 10 May 2016
Available online 19 May 2016

Keywords:
Cyclic imides
Lactams
Acetamides
Antiepileptic
X-Ray diffraction
IR spectroscopy

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.

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],

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http://dx.doi.org/10.1016/j.molstruc.2016.05.031
0022-2860/

and our groups' recent paper reports 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 (Fig. 1).

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 MoKα radiation (λ = 0.7107 Å) and corrected for absorption using the *SADABS* program [15]. Crystals were mounted on a needle and cooled in a stream of N_2 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: $U_{iso}(H) = 1.2U_{eq}(N)$. The hydrogen atoms at carbons were placed in calculated positions and included into the refinement within the riding model with fixed isotropic displacement parameters: $U_{iso}(H) = 1.5U_{eq}(C)$ for CH_3 groups and $1.2U_{eq}(C)$ 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).

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 4000–650 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

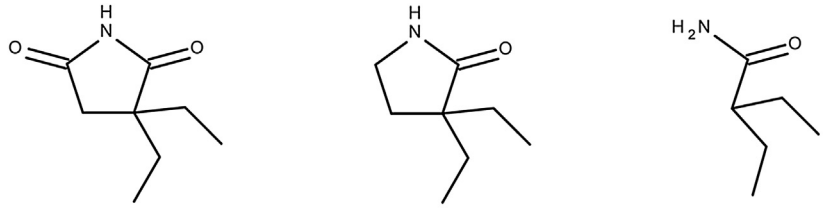
Melting curves were recorded in the OptiMelt MPA100 automated melting point system with digital image processing technology controlled by MeltView ver. 1.107 software (Stanford Research Systems, Sunnyvale, CA). A heating rate of 1 °C/min was used. Since the instrument was factory calibrated at that heating 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 Fig. 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 (Fig. 2D) clearly demonstrate the similarity of the CO-NH fragment and dissimilarity



3,3-diethylpyrrolidine-2,5-dione **1** 3,3-diethylpyrrolidin-2-one **2** 2,2-diethylacetamide **3**

Fig. 1. Structures of the compounds under investigation.