Available online at www.sciencedirect.com
ScienceDirect
Journal of Molecular Structure 878 (2008) 40–49
Journal of MOLECULAR STRUCTURE
www.elsevier.com/locate/molstruc

Weak interactions in barbituric acid derivatives. Unusually steady intermolecular organic "sandwich" complexes. π–π Stacking *versus* hydrogen bonding interactions

Victor N. Khrustalev [a,*], Konstantin A. Krasnov [b], Tatiana V. Timofeeva [c]

[a] *A.N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28, Vavilov Street, Moscow, Russian Federation*
[b] *I.I. Mechnikov St. Petersburg State Medical Academy, Russian Federation*
[c] *Department of Natural Sciences, New Mexico Highlands University, Las Vegas, NM 87701, USA*

Received 7 May 2007; received in revised form 16 July 2007; accepted 26 July 2007
Available online 6 August 2007

Abstract

The 4-methoxy-6,6-dimethyl-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinolin-6-ium (**1**) and 2-(1*H*-indol-3-yl)-1-ethanaminium (tryptaminium) (**2**) salts of 1,3-dimethyl-2,4,6-trioxoperhydro-pyrimidine-5-spiro-6′-{4′-methoxy-7′-(1,3-dimethyl-2,4,6-trioxoper-hydropyrimidin-5-yl)-5′,6′,7′,8′-tetrahydro[1,3]dioxolo[4,5-*g*]naphthalene} (**3**) have been prepared and their structures have been investigated by single-crystal X-ray diffraction analysis. It has been found on the basis of the crystal packing arrangement as well as physical and chemical properties that derivatives **1** and **2** form unusually steady intermolecular sandwich-like complexes both in the crystal and in solution, which are stabilized by weak C—H...*n*(O=C) hydrogen bonds and π–π stacking. The interplay between the intermolecular π–π stacking and strong N—H...O hydrogen bond interactions and its influence on the "sandwich" structures of **1** and **2** are discussed.

Keywords: Barbituric acid derivatives; "Sandwich" conformation; Hydrogen bonds; π–π stacking; X-ray diffraction study

1. Introduction

Weak intra- and intermolecular forces are an important factor affecting shapes of molecules, which plays a vital role in numerous specific phenomena in chemistry and molecular biology [1–4]. Weak non-bonding interactions are useful chemical tools to control stability, conformation, and assembly of molecules [5,6]. It is, therefore, of great interest to determine the strengths and directional propensities of such interactions at an atomic resolution. However, the detection as well as characterization of non-bonding interactions *in situ* is still challenging in fundamental chemistry [7].

In particular, the absolute asymmetric synthesis that affords optically active compounds starting from achiral reactants in the absence of any external chiral agents is of significant interest [8–12]. To enable the absolute asymmetric synthesis with a high reliability, it is necessary to predict and prepare chiral crystals through the self-assembly of achiral molecules [9,11,12]. Such chiral co-crystals are useful as starting materials for the absolute asymmetric synthesis by solid-state reactions [8,10,13–17] as well as nonlinear optical materials [18–21]. Although chiral crystallization of achiral molecules occurs statistically with a low probability of around 5% [9,11,12,22], several interesting series of chiral co-crystals from two different achiral molecules have been prepared [15,16,23–30]. These materials include helical-type co-crystals of tryptamine with various carboxylic acids [24,27–30]. The crystal chirality is induced by the helical packing arrangement in a single direction between the two achiral molecules through intermolecular non-covalent bonds such as hydrogen bonds and π–π interactions, and salt formation. The molecular packing diagrams from X-ray structure analysis suggested

* Corresponding author. Tel.: +7 495 135 9343; fax: +7 495 135 5085.
E-mail address: vkh@xray.ineos.ac.ru (V.N. Khrustalev).

0022-2860/$ - see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.molstruc.2007.07.036

that the tryptamine molecule played an important role in the formation of the helical structure in these crystals.

Several important asymmetric approaches have also been reported for the stereoselective synthesis of tetrahydroisoquinoline and benzyltetrahydroisoquinoline skeletons [31–33].

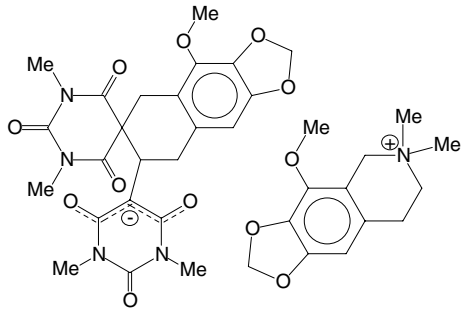
Very recently, we have reported on the structure of 5-arylmethyl-5-cytisylmethylbarbituric acids, which adopt the unusually steady intramolecular "sandwich" conformation both in the solid state and in solution [34,35]. This conformation is stabilized by weak attractive interactions, such as π–π stacking and C—H...π/*n* hydrogen bonds.

We were interested in expanding our studies to related complexes that exhibit modified and controlled π–π stacking and other weak interactions. In view of the aforesaid, herein, we report the preparation of 4-methoxy-6,6-dimethyl-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinolin-6-ium (**1**) and 2-(1*H*-indol-3-yl)-1-ethanaminium (tryptaminium) (**2**) salts of 1,3-dimethyl-2,4,6-trioxoperhydro-pyrimidine-5-spiro-6′-{4′-methoxy-7′-(1,3-dimethyl-2,4,6-trioxoper-hydro-pyrimidin-5-yl)-5′,6′,7′,8′-tetrahydro-[1,3]-dioxolo[4,5-*g*]naphthalene} that contain four extensive planar cyclic π-systems (Chart 1), and explore the influence of different weak interactions and strong N—H...O hydrogen bonds on the mutual disposition of the π-conjugated moieties.

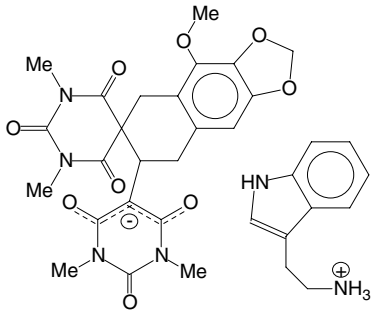
2. Experimental

2.1. General synthetic procedure

The ^{1}H NMR spectra were recorded on a Bruker AM-500 spectrometer at 500 MHz in $CDCl_3$ and DMSO-d_6 solutions. Signals were identified using standard NMR methods of HH-COSY and NOESY.



1



2

Chart 1.

The reactions were monitored with thin-layer chromatography (TLC) [on Silufol UV-254 plates using $CHCl_3$:$CH_3COOC_2H_5$ (5:1) or $CHCl_3$:$CH_3COOC_2H_5$:CH_3COOH (4:2:0.1) solvent mixture], ^{1}H NMR spectroscopy, and elemental analysis.

2.1.1. Synthesis of *1*

A dimethylacetamide solution (10 ml) of cotarnine (2.38 g; 0.01 mol) and 1,3-dimethylbarbituric acid (3.12 g; 0.02 mol) was heated to 160 °C and kept for 15 min. After cooling, the reaction mixture was diluted with a 5% water solution of ammonia (50 ml). The precipitate formed was filtered, and the solution was extracted with chloroform (30 ml). The organic extract was dried with Na_2SO_4 and the solvent was removed in vacuum. The residue was washed with ether and dissolved in hot ethanol (15 ml). Some amount of water was added to the ethanolic solution to promote the crystallization. The solution was left for 48 h at room temperature. Cream-colored crystals were separated by filtration, washed with ethanol and dried in air to afford 530 mg (21.6%) of product. $T_{m.p.} = 281$–282 °C (with decomp.). ^{1}H NMR (500 MHz, $CDCl_3$, 20 °C): $\delta = 2.49 + 3.72$ (dd + dd, ab-system, $J = 14.0$, 2H; C(8)H_2), 2.97 (t, $J = 5.8$, 2H; C(25)H_2), 3.03 + 3.44 (dd, ab-system, $J = 17.0$, 2H; C(5)H_2), 3.01 + 3.06 + 3.15 (s + s + s, 3H + 3H + 6H; 4NCH_3), 3.22 (s, 6H; $N^{(+)}Me_2$), 3.67 (t, $J = 5.8$, 2H; C(24)H_2), 3.94 + 3.99 (s + s, 3H + 3H; 2OCH_3), 3.99 (s, 3H; OCH_3), 4.03 (dd, $J = 9.9$, 1H; C(7)H), 5.78 + 5.81 (dd, ab-system, $J = 1.7$, 2H; C(19)H_2), 5.93 (s, 2H; C(2)H_2), 6.18 (s, 1H; C(26)H), 6.31 (s, 1H; C(9)H). Calcd. for $C_{36}H_{41}N_5O_{12}$ (%): C, 58.77; H, 5.62; N, 9.52. Found (%): C, 58.45; H, 5.71; N, 9.37.

2.1.2. Synthesis of *2*

A solution of tryptamine (0.16 g, 1 mmol) in a 3:1 chloroform/methanol solvent mixture (4 ml) was added to a chloroform solution (10 ml) of the CH-acid **3** (0.5 g, 1 mmol) at 40 °C. The reaction mixture was maintained at 20 °C until the precipitation of a dense residue. The residue was filtered, washed with chloroform, and dried in air to yield the complex **2** as a white crystalline powder (0.64 g, 97%). The crude product (0.3 g) was re-crystallized from ethanol (30 ml, 70%) to give colorless needle-like crystals of **2**. $T_{m.p.} > 299$ °C (with decomp.). ^{1}H NMR (500 MHz, DMSO-d_6, 20 °C): $\delta = 2.29$ (dd, $J^1 = 12.7$, $J^2 = 9.5$, 1H; C(8)H-ax), 2.84 + 3.43 (d + d, ab-system, $J = 17.3$, 1H + 1H; C(5)H_2), 2.94 (s, 3H; NCH_3), 2.96 (s, 3H; NCH_3), 3.00 (s, 6H; 2 NCH_3), 3.02 (q, $J = 6.8$, 2H; Ind-CH_2), 3.08 (q, $J = 6.8$, 2H; NCH_2), 3.53 (dd, $J^1 = 12.7$, $J^2 = 3.5$, 1H; C(8)H-eq), 3.96 (s, 3H; OCH_3), 3.99 (dd, $J^1 = 9.5$, $J^2 = 3.5$, 1H; C(7)H), 5.86 (ab-system, $J = 2.3$, 2H; OCH_2O), 6.21 (s, 1H; C(9)H), 6.96 (dd, $J = 8.1$, 1H; C(22)H), 7.06 (dd, $J = 8.1$, 1H; C(23)H), 7.15 (d, $J = 2.0$, 1H; C(19)H), 7.35 (d, $J = 8.1$, 1H; C(22)H), 7.50 (dd,