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Crystal and Molecular Structure of 2-Amino-5-butyl-3-ethyl-6-methyl-4(3*H*)-pyrimidinone

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Summary. The structure of 2-amino-5-*n*-butyl-3-ethyl-6-methyl-4(*3H*)-pyrimidinone (**1**) has been studied by X-ray diffraction and *ab initio* calculations at the HF/6-31G* level. X-ray analysis established that **1** exists as the amino-oxo tautomer (**AO**) in the solid state, in good agreement with the *ab initio* results. Crystals of **1** are tetragonal (space group $P4_2/n$); the unit cell dimensions are $a = 17.074$ Å, $b = 17.074$ Å, $c = 8.809$ Å, $\alpha = \beta = \gamma = 90°$. The 4-pyrimidinone ring is essentially planar in the crystal, the amino nitrogen and the carbonylic oxygen being located in the plane of the ring. The 2-amino-5-*n*-butyl-3-ethyl-6-methyl-4(*3H*)-pyrimidinone molecules are linked by strong N–H···O intermolecular hydrogen bonds from the NH_2 group of one molecule to the C=O group of an adjacent molecule (N–H···O distance: 2.88 Å).

Keywords. 2-Amino-4-pyrimidinone; Tautomerism; X-Ray crystal structure.

Kristall- und Molekülstruktur von 2-Amino-5-butyl-3-ethyl-6-methyl-4(3*H*)-pyrimidinon

Zusammenfassung. Die Struktur von 2-Amino-5-*n*-butyl-3-ethyl-6-methyl-4(3*H*)-pyrimidinon (**1**) wurde röntgenstrukturanalytisch und mittels *ab intitio* – Berechnungen (HF/6-31G*) untersucht. Die Röntgenstrukturanalyse zeigt, daß **1** als Amino-Oxo-Tautomer (**AO**) vorliegt, was mit den Ergbnissen der Rechnungen übereinstimmt. Die Kristalle von **1** sind tetragonal (Raumgruppe $P4_2/n$) mit den Zellparametern $a = b = 17.074$ Å, $c = 8.809$ Å und $\alpha = \beta = \gamma = 90°$. Der 4-Pyrimidinonring ist im Kristall planar; der Aminstickstoff und der Carbonylsauerstoff liegen in der Ringebene. Die Moleküle der Verbindung **1** werden durch starke intermolekulare Wasserstoffbrücken verbunden, die von der NH_2-Gruppe einer Einheit zur C=O-Gruppe der nächsten reichen (N–H···O – Abstand: 2.88 Å).

Introduction

Studies of tautomerism phenomena have been of interest in many areas of chemistry. 2- and 4-pyrimidinones are the parent compounds of numerous biologically important pyrimidine nucleobases and enzymes [1], and have been extensively studied for identification and structural confirmation as well as for the investigation of their tautomeric nature [2]. It has been recognized that the

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tautomeric form adopted depends on the environment [3]; furthermore, the existence of particular tautomeric forms in certain cases has significant chemical and biological consequences. During the course of investigations on 4-pyrimidinones and related compounds [4], we have determined the crystal structure of 2-amino-5-*n*-butyl-3-ethyl-6-methyl-4(3*H*)-pyrimidinone (**1**). *Ab initio* calculations of the tautomeric forms of **1** are presented and compared with crystallographic data. The study undertaken here potentially can lead to predictions of biologically active tautomeric forms and may be helpful in the formulation of reaction mechanisms.

Results and Discussion

2-Amino-5-*n*-butyl-3-ethyl-6-methyl-4(3*H*)-pyrimidinone (**1**) may occur, in principle, in three different tautomeric forms as a result of both oxo (**O**) $\rightleftharpoons$ hydroxy (**H**) and amino (**A**) $\rightleftharpoons$ imino (**I**) prototropy (Fig. 1). The 2-amino-4-pyrimidinone moiety (isocytosine) appears in many synthetic or naturally occuring compounds exclusively in the amino-oxo tautomeric forms [5], and no other forms (imino, hydroxy) were detected except in nonpolar environments (gas phase, nonpolar matrices) [6]. The above conclusion is upheld by the present study which establishes by X-ray diffraction analysis that **1** exists exclusively as the amino-oxo tautomer (**AO**) in the solid state. The ORTEP diagram of **1** with the crystallographic numbering system is shown in Fig. 2. Positional parameters and isotropic

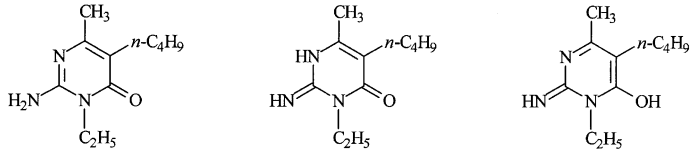

Fig. 1. Tautomeric forms of 2-amino-5-*n*-butyl-3-ethyl-6-methyl-4(3*H*)-pyrimidinone (**1**)

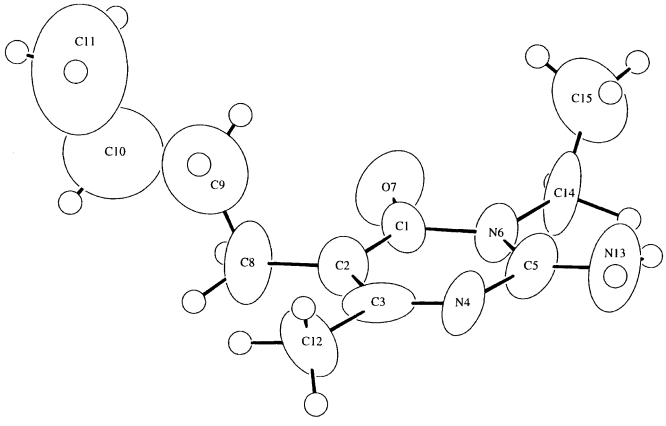

Fig. 2. The molecular structure of **1** including the atomic numbering scheme; displacement ellipsoids are shown at 50% probability level

temperature factors (U_{eq}) are given in Table 1, selected bond distances and angles in Table 2.

The location of the hydrogen atoms on N13 rather than N4 or O7 along with the lengths of the C–N and C–O bonds (Table 2) prove that **1** exists as the **AO** tautomer in the solid state. Bond distances are comparable to those reported for the analogous tautomer of isocytosine [5a]. The rather long C=O bond distance of 1.246 Å and the C5–N13 bond distance of 1.331 Å are typical for this class of compounds [5a–b] and suggest considerable conjugation; the corresponding bond distances in isocytosine are 1.248 Å and 1.324 Å, respectively [5a]. The

Table 1. Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2) of compound **1**

Atom	*x*	*y*	*z*	U_{eq}
C1	0.7154(4)	0.4382(3)	0.2425(8)	0.066(2)
C2	0.6749(4)	0.4929(3)	0.1514(7)	0.066(2)
C3	0.6044(4)	0.5206(3)	0.2004(7)	0.067(2)
N4	0.5713(3)	0.4988(3)	0.3346(6)	0.068(2)
C5	0.6080(3)	0.4471(3)	0.4203(8)	0.066(2)
N6	0.6785(3)	0.4150(2)	0.3774(6)	0.0610(14)
O7	0.7802(2)	0.4078(2)	0.2151(5)	0.090(2)
C8	0.7171(5)	0.5204(5)	0.0092(8)	0.110(3)
C9	0.7707(4)	0.5921(6)	0.0380(10)	0.141(4)
C10	0.8202(8)	0.6185(9)	−0.0905(14)	0.219(6)
C11	0.8656(8)	0.6920(8)	−0.0457(18)	0.270(9)
C12	0.5566(4)	0.5801(4)	0.1119(7)	0.094(2)
N13	0.5768(4)	0.4260(4)	0.5524(8)	0.094(2)
C14	0.7191(4)	0.3578(4)	0.4751(9)	0.090(2)
C15	0.7658(5)	0.3972(5)	0.5979(10)	0.136(3)
H13A	0.5400(37)	0.4576(34)	0.5852(65)	0.091(23)[1]
H13B	0.5916(41)	0.3885(40)	0.6084(78)	0.112(29)[1]
H8A	0.6785(5)	0.5340(5)	−0.0673(8)	0.132[2]
H8B	0.7485(5)	0.4777(5)	−0.0303(8)	0.132[2]
H9A	0.7378(4)	0.6356(6)	0.0688(10)	0.170[2]
H9B	0.8048(4)	0.5798(6)	0.1227(10)	0.170[2]
H10A	0.7875(8)	0.6297(9)	−0.1779(14)	0.263[2]
H10B	0.8566(8)	0.5773(9)	−0.1182(14)	0.263[2]
H11A	0.8974(8)	0.7088(8)	−0.1294(18)	0.405[2]
H11B	0.8984(8)	0.6807(8)	0.0400(18)	0.405[2]
H11C	0.8294(8)	0.7329(8)	−0.0195(18)	0.405[2]
H12A	0.5093(4)	0.5917(4)	0.1662(7)	0.141[2]
H12B	0.5438(4)	0.5590(4)	0.0139(7)	0.141[2]
H12C	0.5866(4)	0.6273(4)	0.0994(7)	0.141[2]
H14A	0.7539(4)	0.3261(4)	0.4132(9)	0.107[2]
H14B	0.6808(4)	0.3231(4)	0.5210(9)	0.107[2]
H15A	0.7913(5)	0.3582(5)	0.6589(10)	0.204[2]
H15B	0.7314(5)	0.4277(5)	0.6605(10)	0.204[2]
H15C	0.8044(5)	0.4307(5)	0.5528(10)	0.204[2]

[1] Refined isotropically; [2] not refined

Table 2. Selected geometric parameters (bond distances in Å; bond angles in degrees) in **1**

Atom	Exp.	HF/6-31G*	Atom	Exp.	HF/6-31G*
C1-C2	1.413	1.452	C1-C2-C3	118.8	117.8
C2-C3	1.362	1.352	N6-C1-C2	116.6	116.0
C3-N4	1.362	1.371	N4-C5-N6	121.7	124.1
N4-C5	1.319	1.283	C1-C2-C3-N4	1.2	0.0
C5-N6	1.376	1.358	C3-N4-C5-N6	−1.2	−0.6
N6-C1	1.402	1.401	C1-N6-C5-N13	−178.1	−179.7
C1-O7	1.246	1.206	N4-C5-N6-C14	−180.1	−176.7
C5-N13	1.331	1.371	C1-C2-C3-C12	179.1	179.2
N6-C14	1.475	1.468	C5-N6-C1-O7	176.1	176.6

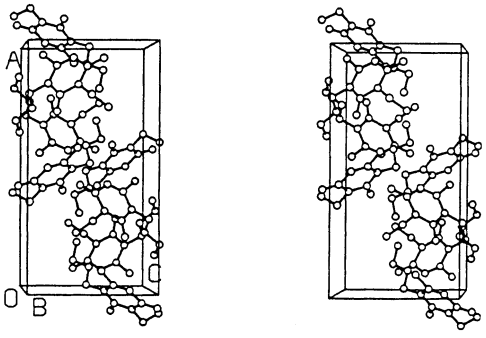

Fig. 3. Packing diagram of **1**

pyrimidinone ring and its substituents remain almost coplanar. The sum of all bond angles is 359.9° for N6 and 359.6° for N13, and thus their configuration is essentially planar. The largest deviation of a ring atom from the least-squares plane through the six ring atoms is 0.021 Å for C5 (C1 deviates by 0.020 Å), and the largest deviation of a substituent is 0.046 Å for O7.

The molecules of **1** are stacked in the unit cell around a center of symmetry and are connected by intermolecular N–H···O hydrogen bonds from the NH_2 group of one molecule to the C=O group of an adjacent molecule (N–H···O distance: 2.88 Å; N–H–O angle: 159.9°; see Fig. 3). The shift of the C=O stretching frequency to lower wavenumbers in the IR spectrum of **1** (KBr pellet; see Experimental) is consistent with strong H-bonding in the crystal [7]. Similarly, a pronounced concentration-dependence has been noted for the ^{1}H NMR signal of the exocyclic NH_2 group in solution; its chemical shift increases by 1 ppm when the sample concentration varies from 1 to 5%, presumably due to H-bonding through N–H···N and/or N–H···O hydrogen bonding, which is reduced upon dilution [8].

Knowledge of the energetics of tautomerism can provide useful information on the intrinsic stability of tautomers. The **AO** form is predicted to be the most stable tautomer of **1** in the gas-phase (Table 3) at the HF/6-31G* level of theory [9], in good agreement with the crystallographic data. There is excellent correspondence between the experimental and the calculated structure (see Table 2). Most

Table 3. Total (a.u.) and relative energies (kcal/mol) of the tautomers of **1** calculated at the HF/6-31G* level[1]

	2-Amino-5-*n*-butyl-3-ethyl-6-methyl-4(*3H*)pyrimidinone **1**		
	AO (N-H_3)	**IO**	**IH** (N-H_3)
HF/6-31G*	−665.864197	−665.852320	−665.804095
ΔE	0.00	7.47	33.71

[1] Structures were fully optimized using Spartan 4.0 (Wavefunction Inc., Irvine, CA) implemented on a cluster of SGI Indigoes.

differences between *ab initio* calculations and experimental data on the bond distances for non-hydrogen atoms are within 0.021 Å on the average (0.001 to 0.047 Å). The mean difference in bond angles between non-hydrogen atoms is approximately 1.4°.

Experimental

2-Amino-5-n-butyl-3-ethyl-6-methyl-4(3H)-pyrimidinone (**1**)

The title compound was obtained as a byproduct (15%) in the condensation of *N*-ethylguanidine with ethyl *n*-butylacetoacetate [4a]. Single crystals suitable for X-ray analysis were grown by slow evaporation of a saturated solution of **1** in chloroform (m.p. 189°C). The ^{13}C NMR signals of **1** are tentatively assigned based on chemical shift, relative intensity, and DEPT ^{13}C NMR spectra. IR (KBr): $\nu = 3339$, 3112, 2928, 1683, 1630, 1527, 1199 cm^{-1}; ^{13}C NMR ($CDCl_3$, 300 MHz): $\delta = 162.23$ (C1), 158.38 (C5), 151.89 (C3), 114.09 (C2), 36.86 (C14), 31.05 (C8), 25.86 (C9), 22.80 (C10), 20.96 (C12), 13.96 (C15), 12.48 (C11) ppm; MS (EI): *m/z* = 209 (21), 180 (9), 167 (29), 166 (100), 139 (13), 138 (25), 96 (34), 71 (7), 55 (19), 43 (18), 42 (14); $C_{11}H_{19}N_3O$.

Crystal structure determination

A single crystal of **1** measuring $0.2 \times 0.2 \times 0.3$ mm^3 was chosen for X-ray measurements and was mounted by epoxy on a glass fiber. Crystal data: $C_{11}H_{19}N_3O$; tetragonal; space group $P4_2/n$; unit cell dimensions: $a = 17.074$ Å, $b = 17.074$ Å, $c = 8.809$ Å, $\alpha = \beta = \gamma = 90°$, $V = 2568.00$ Å^3, $D_{calc} = 1.088$ g/cm^3. Data were collected on a Siemens P3 diffractometer using monochromatized Mo radiation. The structure was solved by direct methods and refined by full-matrix least-squares techniques on F^2 with SHELXL-93 [10]. The intensity measurements were carried out by the $\omega - 2\theta$ scan technique (scan rate: 2°/min; scan range up to $2\theta = 45°$) and were corrected for decay effects; no absorption corrections were made. A total of 1688 unique reflections were collected, of which 696 reflections were observed with $I > 2\sigma(I)$. Final refinement with 144 parameters converged at $R = 0.0711$ and $R_W = 0.2012$ with goodness of fit = 1.023. The mobile hydrogen atoms (H13A and H13B) were found from the difference density maps and were refined with isotropic temperature factors.[1]

[1] Additional material to the structure determination may be ordered from Fachinformationszentrum Karlsruhe, Gesellshaft für wissenschaftlich-technische Information mbH, D-76344 Eggenstein-Leopoldshafen, Federal Republic of Germany, referring to the deposition number CSD-59454, the names of the authors, and the citation of the present paper.

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