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Tautomeric and *Ab initio* Studies of 3-Amino-4*H*-1,2,4-oxadiazolin-5-one

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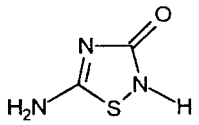
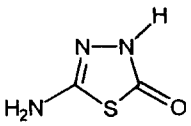
We have recently reported on the synthesis and tautomeric behavior of 5-amino-2*H*-1,2,4-thiadiazolin-3-one (**1**)[1-5] and 5-amino-3*H*-1,3,4-thiadiazolin-2-one (**2**)[1,6] within the framework of our systematic studies of biologically active analogs of pyrimidines and their derivatives. Compound **1** is an analog of cytosine, in which the C=C bond of cytosine is replaced with sulfur. The analogy of the C=C bond in heterocyclic benzenoids (cytosine) and either the divalent sulfur or oxygen in their sulfur (oxygen) containing counterparts is well-known, both in benzenoid and also in heterocyclic chemistry. Compound **2** is an isomer of 5-amino-2*H*-1,2,4-thiadiazolin-3-one. Thus, compounds **1** and **2** can exist in equilibria of four possible tautomeric forms, as can cytosine. In order to understand their reactivity, it is necessary to determine the stable tautomeric structure. Particularly in biologically active compounds, investigation of the relative stability of tautomers is important in structure-biological activity relationship studies.



1

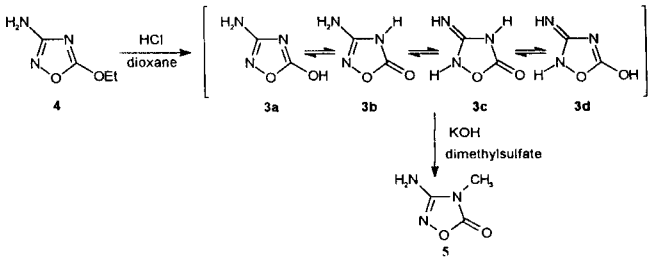


2

The spectroscopic study (^{13}C and ^{1}H nmr and ir) and theoretical calculations supported that compound **1**[4] and 5-acylamino-2*H*-1,2,4-thiadiazolin-3-ones[3] exist as lactam forms in solution. Compound **2**[7,8] and 5-acylamino-3*H*-1,3,4-thiadiazolin-2-ones[6] also exist as lactam forms, on the basis of ir, ^{13}C, ^{15}N and ^{1}H NMR[6-8] and theoretical calculations.[6] As an extension of these studies, we report our study of the tautomerism of 3-amino-4*H*-1,2,4-oxadiazolin-5-one (**3**) through spectroscopic investigation and theoretical calculations. By replacement of sulfur with oxygen, compound **3** is an analog of compound **1**. The study of 3-amino-4*H*-1,2,4-oxadiazolin-5-one only dealt with synthesis,[9] not with its structure and reactivity. Thus, we promptly studied the tautomeric structure of **3**.

3-Amino-4*H*-1,2,4-oxadiazolin-5-one (**3**) was obtained by cleavage of the ethyl group in 3-amino-5-ethoxy-1,2,4-oxadiazole (**4**)[9] with dioxane-hydrochloric acid, as shown in Scheme **1**. The melting point of **3** is higher than the reported value[9] by 15 °C, however, the spectroscopic results are identical with those previously reported.[9] In addition, the elemental analyses matched the theoretical values. The synthesis of **4** was achieved by following the reported procedure.[9] It was confirmed by comparing the melting point and spectroscopic results with those in the literature.[9] These, along with the elemental analyses, matched the theoretical values.

3-Amino-4*H*-1,2,4-oxadiazolin-5-one (**3**) can theoretically exist in four tautomeric forms, **3a-d**. The stable tautomeric form was determined by spectroscopic methods. The spectroscopic results are shown in Scheme 2. The ratio of peak areas between 6.22 and 11.39 ppm (2 : 1) in the ^{1}H NMR spectrum indicates that **3** exists as either the lactam or the lactim, among the four possible tautomers. In the ir, a strong diagnostic carbonyl band and the typical stretching bands of the amino group appeared at 1760 cm^{-1}, 3400 and 3250 cm^{-1} respectively. These data imply that **3** exists as the lactam form.



4 3a 3b 3c 3d 5

Scheme 1. Synthesis of 3-amino-4*H*-1,2,4-oxadiazolin-5-one and derivative.

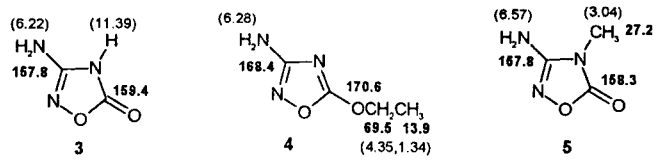
Table 1. Relative energies (in Kcal/mol) and total energies (in a.u.) for **3a-d** tautomers

	3a	**3b**	**3c**	**3d**
[a] MP2//HF/6-31G*	8.04	0.00	9.61	55.01
	(−391.58260)[b]	(−391.59542)	(−391.58042)	(−391.50776)
[a] MP2//HF/3-21G*	16.94	0.00	11.57	61.00
	(−389.03220)	(-389.05920)	(−389.04077)	(-388.96199)

[a] MP2//HF/6-31G* (3-21G*) represents a MP2 single point calculation at the HF optimized geometry with 6-31G* (3-21G*) basis set. [b] The values in parentheses are total energies.

To confirm this result, a comparative ^{13}C NMR experiment was performed. ^{13}C NMR spectroscopy is widely utilized for distinguishing between lactams and lactims. The difference of chemical shift between a lactam and a lactim is not as clear as that between a thione and a thiol. Thus, interpretation of only the absolute chemical shifts can easily lead to erroneous conclusions. A standard compound (lactam or lactim) is required for chemical shift comparisons. As an authentic lactam compound, 3-amino-4-methyl-1,2,4-oxadiazolin-5-one (**5**) was synthesized. The NH proton of **3** is very acidic, as are those of 5-amino-2*H*-1,2,4-thiadiazolin-3-one (**1**)[4] and 5-amino-3*H*-1,3,4-thiadiazolin-2-one (**2**).[6,7] The *N*-methylation of (**3**) followed the same method[1,4] as those of **1** and **2**. ^1H and ^{13}C NMR, ir, and elemental analyses proved the identity of 3-amino-4-methyl-1,2,4-oxadiazolin-5-one. In the ir spectrum, the lactam carbonyl group appears as a diagnostic strong band at 1763 cm^{-1}, while the C=N band appears as a weak absorption at 1518 cm^{-1}. ^1H nmr indicates a methyl group at 3.04 ppm, instead of NH at 11.39 ppm and NH_2 group at 6.57 ppm. NCH_3 also appeared at 27.2 ppm in ^{13}C NMR. Furthermore, the methyl signal at 3.04 ppm was associated with signals at both 158.3 ppm (C5) and 157.8 ppm (C3) in ^1H-^{13}C long range correlation (HMBC[10] experiment) for the confirmation of structure **3**. All these spectral data support the structure of 3-amino-4-methyl-1,2,4-oxadiazolin-5-one (**5**). In addition, its elemental analyses were satisfactory.

^{13}C NMR data were compared among compounds **3**, **4** and **5**. To assign the ^{13}C chemical shifts of the ring carbons in **4**, an HMBC experiment was performed. The experiment was optimized for a long-range ^1H-^{13}C coupling constant of 7 Hz. These traces show that the CH_2 group is associated with the carbon absorbing at 170.6 ppm (C(5)). Consequently, the ^{13}C chemical shifts of C(5) and C(3) were



unit: ppm, ( ): ^1H NMR, bold: ^{13}C NMR

IR (KBr, cm^{-1}):

Compound (**3**): 3400, 3250 (NH), 3000, 1780 (C=O), 1680, 1540 (C=N).

Compound (**4**): 3400, 3250 (NH), 3050 (CH), 1680, 1640, 1480 (C=N) 1050 (C=O).

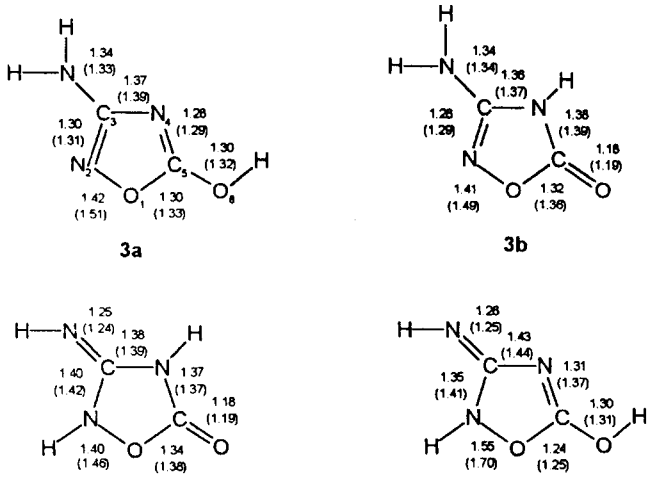
Compound (**5**): 3372, 3186 (NH), 2910 (CH), 1763 (C=O), 1650, 1518 (C=N).

Scheme 2. The ^1H, ^{13}C NMR and ir spectra of 3-amino-4*H*-1,2,4-oxadiazolin-5-one (**3**), 3-amino-5-ethoxy-1,2,4-oxadiazole (**4**), and 3-amino-4-methyl-1,2,4-oxadiazolin-5-one (**5**).

170.6 and 168.4 ppm respectively. However, the chemical shift of ring carbons in compound **5** can not be assigned even with the HMBC experiment, since the methyl group is associated with both two ring carbons, as mentioned above. The chemical shifts of the ring carbons of compound **3** and **5** are more or less similar, atom by atom. The difference of chemical shifts between **4** and **3** at C(5) is very large (~10 ppm), while the difference of chemical shifts between **3** and **5** at C(5) is negligible (~1 ppm). ^{13}C NMR investigations of compound **1**[4], **2**[6,7] and 2-pyridone[11] corroborated this finding and revealed that the chemical shift of the *N*-methylation compound shows only small shift (0.5-3.4 ppm) differences with those of **1, 2** and 2-pyridone, respectively. It could be concluded that the stable tautomeric form of compound **3** is the lactam form, on the basis of comparative studies of ^{13}C NMR spectra.

This result is also supported by *ab initio* calculations with the GAUSSIAN 94 package[12] on a Cray Y-MP C916 supercomputer. Standard 3-21G* and 6-31G* basis sets[13] were used to optimize geometries at the Hartree-Fock level. Second-order Moller-Pleset perturbation (MP2) calculations were carried out at the HF optimized geometries to obtain improved energy comparisons. The optimized geometries of the four tautomers are shown in Scheme 3.

The optimized bond distances at both the 6-31G* and 3-21G* levels are close to each other, with the exception of the O(1)-N(2) distance. The O(1)-N(2) distance at the 6-31G* level was computed to be 0.1 Å shorter on average



Scheme 3. Optimized bond distances (in Å) for **3a-d** at the HF/6-31G* and HF/3-21G* levels. The values in parentheses are the HF/3-21G* level.

than at the 3-21G* level. Significant features of the optimized geometries of the four tautomers also occur in the C(5)-O(6) and C(5)-N(4) bond distances. The C=O distance of 1.18 Å in **3b** is increased by 0.12 Å to the C-O single bond distance of 1.30 Å in **3a**. The N(4)-C(5) bond single bond distance of 1.38 Å in **3b** is shortened by 0.1 Å to the double bond character of 1.28 Å in **3a**. These results are in good agreement with the other *ab initio* studies on the tautomerism of pyrimidine bases[14,15] and their 5-membered analogs.[4,6] The calculated total energies and relative energies of the tautomers at the MP2 level are given in Table 1. The most stable tautomer is **3b** at both the 3-21G* and the 6-31G* levels, which corresponds to our experimental results. The relative energy difference between **3b** and the others is larger than 8 Kcal/mol by both basis sets calculations; this is large enough to ensure that it exists only as the most stable tautomeric form.

Experimental

All melting points were obtained using an electrically heated Thomas-Hoover capillary melting point apparatus and were uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX-400 spectrometer and IR spectra on a Jasco Report-100 infrared spectrophotometer. Elemental analyses were carried out on an Elementar Analysensysteme GmbH Vario EL at the Korea Basic Science Institute, Seoul, Korea. Most of the commercially available starting materials and solvents were purchased from Aldrich Chemical Company.

3-Amino-5-ethoxy-1,2,4-oxadiazole (4) was prepared by the procedure described in the literature.[9] mp: 127-129 °C (lit.[9] 128-129 °C); ^{1}H NMR (DMSO-d_6, δ, ppm): 6.28 (br, 2H, NH_2), 4.35 (q, 2H, CH_2, J=7.0), 1.34 (t, 3H, CH_3, J=7.1); ^{13}C NMR (DMSO-d_6, δ, ppm): 170.6 (C-OEt), 168.4 (C=N), 69.5 (CH_2), 13.9 (CH_3); ir (KBr, υ, cm^{-1}): 3400, 3250 (NH), 3050 (CH), 1680, 1640, 1480 (C=N), 1050 (C-O). Anal. Calcd. for $C_4H_7N_3O_2$: C, 37.21; H, 5.46; N, 32.54. Found: C, 36.75; H, 5.48; N, 33.59.

3-Amino-4*H*-1,2,4-oxadiazolin-5-one (3); 3-Amino-5-ethoxy-1,2,4-oxadiazole (**4**) (0.94 g, 70 mmol) was dissolved in dioxane (20 mL) and HCl (0.75 mL, 70 mmol) was added. The reaction mixture was refluxed for 2.5 hrs. Solvent was distilled off under the reduced pressure. The reaction residue was recrystallized from water to afford 3-amino-4*H*-1,2,4-oxadiazolin-5-one (**3**) (0.2 g, 26%). mp: 208-210 °C (lit.[9] 195-196 °C); ^{1}H NMR (DMSO-d_6, δ, ppm): 11.39 (br, 1H, NH), 6.22 (br, 2H, NH_2); ^{13}C NMR (DMSO-d_6, δ, ppm): 159.4, 157.8; ir (KBr, υ, cm^{-1}): 3400, 3250 (NH), 3000, 1760 (C=O), 1680, 1540 (C=N); Anal. Calcd. for $C_2H_3N_3O_2$: C, 23.77; H, 2.99; N, 41.58. Found: C, 23.89 (23.77)[9]; H, 3.06 (3.08)[9]; N, 42.72. (41.39)[9].

3-Amino-4-methyl-1,2,4-oxadiazolin-5-one (5); 3-Amino-4*H*-1,2,4-oxadiazolin- 5-one (**3**) (1 g, 10.7 mmol) was dissolved in 5 mL KOH solution (0.6 g, 9.9 mmol) and dimethylsulfate (1.1 mL, 11.9 mmol) was added. It was stirred for 24 hrs at room temperature and stored in refreigerator for 2 days. The precipitate was filtered and recrystallized from water to afford 3-amino-4-methyl-1,2,4-oxadiazolin-5-one (**5**) (0.1 g, 11%); mp: 156-158 °C; ^{1}H NMR (DMSO-d_6, δ, ppm): 6.57 (br, 2H, NH_2), 3.04 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, δ, ppm): 158.3, 157.8, 27.2 (CH_3); ir (KBr, υ, cm^{-1}): 3372, 3186 (NH), 2910 (CH), 1763 (C=O), 1650, 1518 (C=N); Anal. Calcd. for $C_3H_5N_3O_2$: C, 31.31; H, 4.38; N, 36.51. Found: C, 30.96; H, 4.59; N, 35.23.

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