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Conformational Analysis of 3-Acetylamino-5,6-Dihydrouracils by DFT Computations †

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Abstract

3-Acetylamino-6-aryl-5,6-dihydrouracils were found to exist in DMSO-d_6 solution as mixtures of four rotamers due to hindered rotation around the adjacent N-N (2 major rotamers, 96%) and C-N (2 minor rotamers, 4%) bonds. To explain these NMR spectroscopic data, thermodynamic and kinetic parameters for interconversion of all the rotamers of 3-acetylamino-5,6-dihydrouracil as a model compound were determined using the DFT B3LYP/6-311++G(d,p) method in the gas phase and DMSO solution.

Keywords: 3-acetylamino-5,6-dihydrouracils; hindered rotations; conformational analysis; DFT calculations

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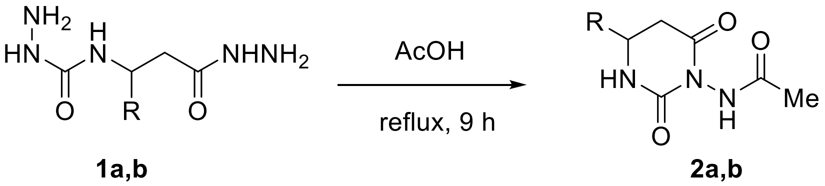
1. Introduction

3-Aminohexahydropyrimidine-2,4-diones (3-amino-5,6-dihydrouracils) are representatives of an interesting type of uracil derivatives. For example, they show various biological activities such as anti-epileptogenic [1] and herbicidal properties [2], HLGPa and TNF-α inhibitory activities [3,4]. However, in contrast to 3-aminohydantoins [5–7], 3-amino-5,6-dihydrouracils remain underexplored to date [8–12].

Recently, we developed a novel approach to derivatives of 6-substituted 3-amino-5,6-dihydrouracils involving the acid-catalyzed cyclization of hydrazides of β-(4-semicarbazido)carboxylic acids **1** [13]. In particular, refluxing hydrazides **1a,b** in AcOH for 9 h resulted in 3-acetylamino-5,6-dihydrouracils **2a,b** in yields of 84–87% (Scheme 1).



1-2 a R = Ph, **b** R = 4-MeC_6H_4.

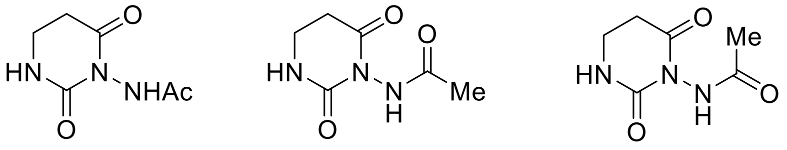
Scheme 1. Preparation of 3-acetylamino-5,6-dihydrouracils **2a,b**.

It is noteworthy that the ^{1}H and ^{13}C NMR spectra of compounds **2a,b** in DMSO-d_6 showed the presence of four sets of signals of similar protons and carbons with a huge predominance of two ones (96 mol%). This was explained by the existence of uracils **2a,b** as mixtures of 4 rotamers due to restricted rotation around the adjacent N-N and C-N bonds. Ratios of the rotamers for the crude compounds **2a,b** in DMSO-d_6 solution at 303K were 50:46:2.1:1.9 and 51:45:2.1:1.9, respectively (^{1}H NMR data). It should be noted that recrystallization of these compounds did not change the rotamer ratios.

Although restricted rotation around the amide C-N bond due to its partial double-bond character that arises from resonance between the nitrogen lone pair and the carbonyl group is well known [14], hindered rotation around the N-N bond giving atropoisomers is not trivial phenomenon [15,16]. To study this type of atropoisomerism in 3-acetylamino-5,6-dihydrouracils, the DFT B3LYP/6-311++G(d,p) calculations were performed. Herein, we report on the results obtained.

2. Results and Discussion

First of all, the thermodynamic characteristics of interconversion of all the rotamers of 6-unsubstituted dihydrouracil **3** (Figure 1) as a model compound were calculated by the DFT B3LYP/6-311++G(d,p) method in the gas phase and DMSO solution using the polarizable continuum model (PCM).



3 *s-cis*-conformer of **3** *s-trans*-conformer of **3**

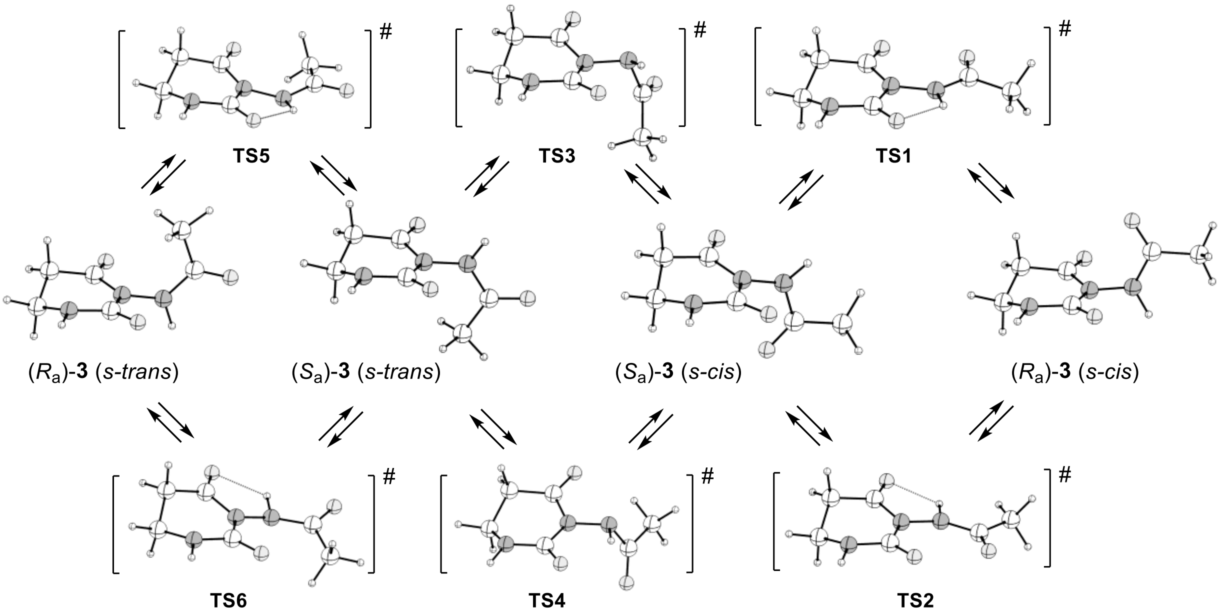
Figure 1. Structure 3-acetylamino-5,6-dihydrouracil **3** and its *s-cis* and *s-trans* conformers relative to the amide C-N bond.

The computations showed that the *s-cis* isomers relative to the amide C-N bond are significantly more stable than the corresponding *s-trans* isomers both in the gas phase and in DMSO solution (Scheme 2, Table 1).

Table 1. Changes in the electron energy (ΔE, kcal/mol) and the Gibbs free energy (ΔG, kcal/mol) during rotation around the N-N and C-N bonds in 3-acetylamino-5,6-dihydrouracil (**3**) in the gas phase and in DMSO solution.[a]

Rotamer or Transtion State	The Gas Phase		DMSO Solution	
	ΔE	**ΔG** [b]	**ΔE**	**ΔG** [b]
(S_a)-3 (*s-cis*)	0.00	0.00	0.00	0.01
(R_a)-3 (*s-cis*)	0.72	0.76	0.08	0.00
(S_a)-3 (*s-trans*)	2.47	2.53	1.61	1.66
(R_a)-3 (*s-trans*)	2.43	2.58	1.77	1.99
TS1	17.45	18.73	17.18	18.14
TS2	18.19	19.51	17.90	18.96
TS3	17.45	18.73	18.98	20.20
TS4	15.73	17.56	18.10	19.32
TS5	16.53	18.50	18.66	19.95
TS6	16.81	18.70	19.14	20.38

[a] According to the DFT B3LYP/6-311++G(d,p) calculations using the polarizable continuum model.
[b] 298 K and 1 atm.



Scheme 2. Conformational changes in 3-acetylamino-5,6-dihydrouracil (**3**) during rotation around the N-N and C-N bonds.

Clockwise or counterclockwise rotation around the N-N bond in the *s-cis*-isomer of uracil **3** gave two energetic minima [(S_a)- and (R_a)-enantiomers] and two transition states (**TS1** and **TS2**). The both atropoisomers are very similar in stability, particularly in DMSO (Table 1). Computations revealed that the planes formed by the C(2)-N(3)-C(4) fragment and the acetylamino group are almost orthogonal. For example, in DMSO, the C(2)-N(3)-NH-C(O) dihedral angle is 88.3° for (S_a)-enantiomer and 90.0° for (R_a)-enantiomer. The interconversion between these enantiomers occur through rather high energy barriers ($\Delta G^{\#}$ = 17.97–19.51 kcal/mol in the gas phase and $\Delta G^{\#}$ = 18.14–18.97 kcal/mol in DMSO; 298 K, 1 atm). Analogously, two energetic minima and two transition states (**TS5** and **TS6**) were found during rotation around the N-N bond in the *s-trans*-isomer of uracil **3** (Scheme 2) with the energy barriers $\Delta G^{\#}$ in the ranges of 15.92–16.17 and 18.02–18.72 kcal/mol for the gas phase and DMSO solution, respectively (298 K, 1 atm).

Rotation around the amide C-N bond was studied using the *s-cis*-(S_a)-rotamer of **3** as an example. This rotation in clockwise and counterclockwise directions resulted in the *s-trans*-(S_a)-rotamer of **3** and proceeded through the transition states **TS3** and **TS4** with $\Delta G^{\#}$ = 15.02–18.73 kcal/mol (the gas phase) and $\Delta G^{\#}$ = 17.70–20.20 kcal/mol (DMSO solution) (298 K, 1 atm).

It should be noted that intrinsic reaction coordinate (IRC) analysis demonstrated that all the found transition states (**TS1-6**) connect the desired minima. Figure 2 shows changes in the Gibbs free energy during rotation around the N-N and C-N bonds in dihydrouracil **3** in DMSO solution.

Thus, the computational data show that the hindered rotations around the N-N and C-N bonds of 3-acetylamino-5,6-dihydrouracil (**3**) could result in racemic mixtures of atropoenantiomers possessing *s-trans*- or *s-cis*-configuration with predominance of the latter. Taking into account these data, next we performed the DFT B3LYP/6-311++G(d,p) computations for 3-acetylamino-6-(4-methylphenyl)-5,6-dihydrouracil (**2b**) (DMSO solution) using the polarizable continuum model (PCM). The hexahydropyrimidine ring of this compound can adopt two stable conformations with a pseudo-equatorial and a pseudo-axial orientation of the 4-methylphenyl group. The calculations revealed that in the case of *s-cis* isomers relative to the amide C-N bond, conformers with the pseudo-equatorial aryl group were more stable in DMSO (ΔG = 1.54–1.56 kcal/mol).

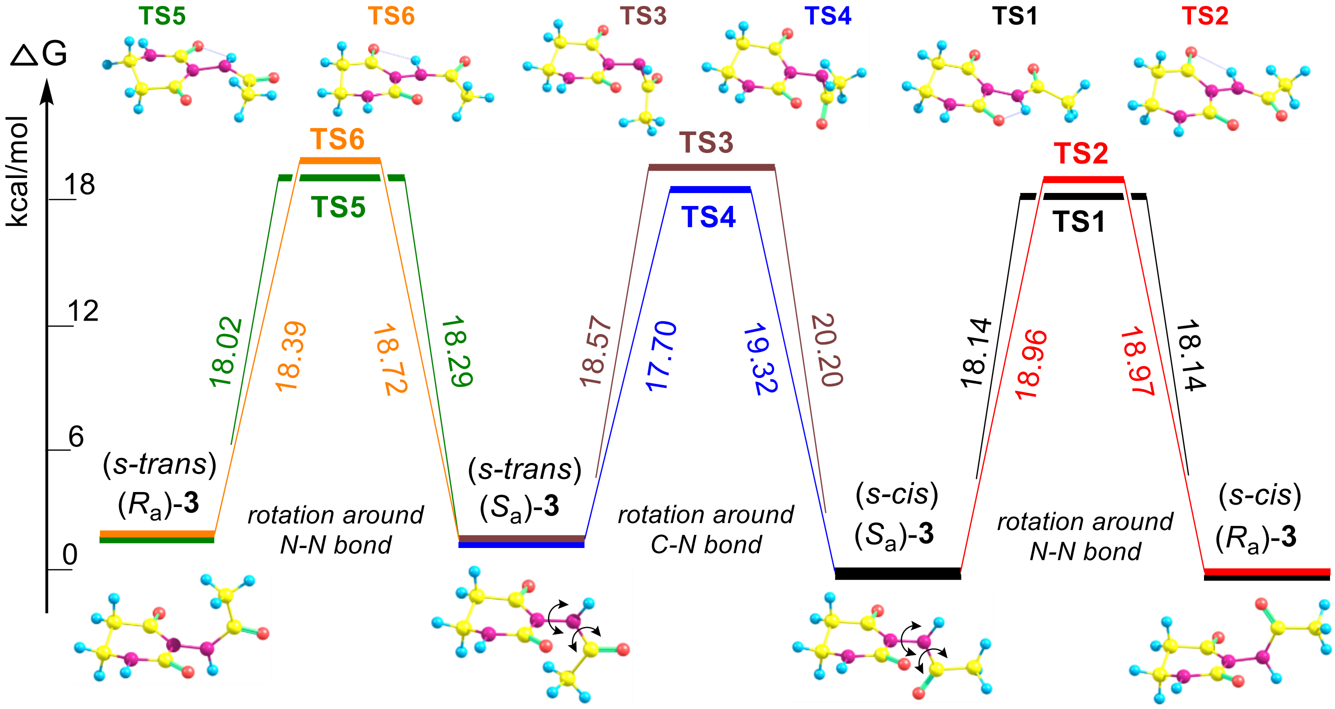
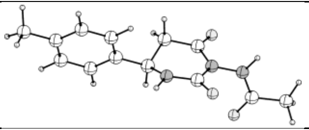
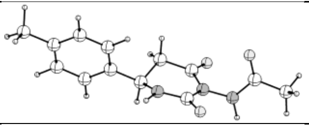
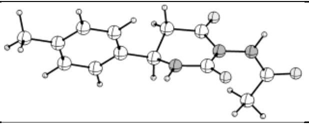
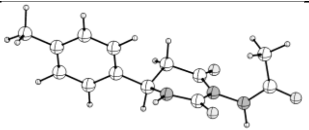


Figure 2. Changes in the Gibbs free energy during rotation around the N-N and C-N bonds in dihydrouracil **3** in DMSO solution.

In general, the DFT computations for dihydrouracil **2b** possessing pseudo-equatorial orientation of the aryl group gave results similar to those for compound **3**. Indeed, the rotations around the N-N and C-N bonds in uracil (6*R*)-**2b** with the pseudo-equatorial aryl group result in 4 rotamers. The 2 rotamers with *s-cis* conformation of the C-N bond are more stable than the 2 rotamers with *s-trans* conformation (Table 2).

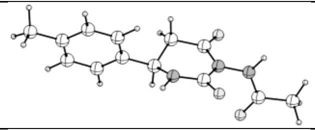
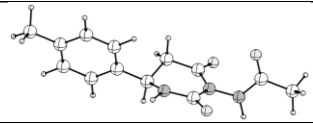
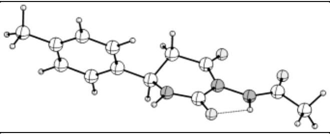
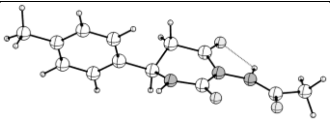
Table 2. Changes in the electron energy (ΔE, kcal/mol) and the Gibbs free energy (ΔG, kcal/mol) during rotation around the N-N and C-N bonds in uracil (6*R*)-**2b** in DMSO solution.[a]

Rotamer	Structure	ΔE	ΔG [b]
(6*R*,S_a)-**2b** (*s-cis*)		0.00	0.53
(6*R*,R_a)-**2b** (*s-cis*)		0.06	0.00
(6*R*,S_a)-**2b** (*s-trans*)		1.71	1.49
(6*R*,R_a)-**2b** (*s-trans*)		1.82	2.03

[a] According to the DFT B3LYP/6-311++G(d,p) calculations using the polarizable continuum model.
[b] 298 K and 1 atm.

Clockwise or counterclockwise rotation around the N-N bond in the *s-cis* conformer of uracil (6*R*)-**2b** gives two energetic minima [(6*R**,S_a*)- and (6*R**,R_a*)-diastereomers] and two transition states (**TS1** and **TS2**) (Table 3). IRC analysis showed that the transition states connect the desired minima. Computations demonstrated that the $(6R^*,R_a^*)$-diastereomer is a little more stable (ΔG = 0.53 kcal/mol) than the $(6R^*,S_a^*)$-diastereomer. The energy barriers ($\Delta G^{\#}$) between the isomers are in the interval of 17.65–19.17 kcal/mol. It is noteworthy that these values are in excellent agreement with the value of restricted rotation barrier around the N-N bond for this compound estimated using ^{1}H NMR spectroscopic data at different temperatures ($\Delta G^{\neq}$ = 19.6 kcal/mol; DMSO-d_6) [13].

Table 3. Changes in the electron energy (ΔE, kcal/mol) and the Gibbs free energy (ΔG, kcal/mol) during rotation around the N-N bond in dihydrouracil (6*R*)-**2b** (*s-cis* conformer) in DMSO solution.[a]

Rotamer or Transition State	Structure	ΔE	ΔG [b]
$(6R,S_a)$-**2b** (*s-cis*)		0.00	0.53
$(6R,R_a)$-**2b** (*s-cis*)		0.06	0.00
TS1		17.10	18.18
TS2		17.89	19.17

[a] According to the DFT B3LYP/6-311++G(d,p) computations (PCM). [b] 298 K and 1 atm.

The values of the calculated hindered rotation barriers indicate that the all rotamers of uracil **2b** are in equilibrium in DMSO at room temperature, but their interconversion is rather slow on the NMR time scale and they can be observed separately by NMR spectroscopy. In this case, one would expect that the rotamer ratio should follow to the calculated stability order: $(6R,R_a)$-**2b** (*s-cis*) > $(6R,S_a)$-**2b** (*s-cis*) >> $(6R,R_a)$-**2b** (*s-trans*) > $(6R,S_a)$-**2b** (*s-trans*) (Table 2). Indeed, this is consistent with the NMR data for this compound (see above).

A comparison of the barriers of rotation around the N-N bond for uracils **3** and **2b** (Table 1 vs. Table 3) shows that the substituent at the C6 does not significantly affect the barrier value.

3. Conclusions

In summary, conformational analysis of two 3-acetylamino-5,6-dihydrouracils was performed using the DFT B3LYP/6-311++G(d,p) method. It was found that these compounds exist as mixtures of 4 rotamers due to restricted rotations around the N-N and C-N bonds. The thermodynamic and kinetic parameters for interconversion of the all rotamers of 6-unsubstituted dihydrouracil were determined in the gas phase and DMSO solution using the polarizable continuum model (PCM). The calculations showed that the *s-cis* isomers relative to the amide C-N bond are significantly more stable than the corresponding *s-trans* isomers. The interconversion between the all rotamers are characterized by fairly high energy barriers (about 18–20 kcal/mol). The DFT calculations for 3-acetylamino-6-(4-methylphenyl)-5,6-dihydrouracil in DMSO solution (PCM) gave results similar to those for the 6-unsubstituted analog.

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References

1. Jones, K.A.; Weaver, D.F.; Tiedje, K.E. Dihydrouracil Compounds as Anti-Ictogenic or Anti-Epileptogenic Agents. *Patent* WO 2004009559, 2004; *Chem. Abstr*. **2004**, *140*, 146155.
2. Loux, H.M. 3-amino-5,5-dihalo-6-alkyl-6-alkoxy Hydrouracils. *Patent* US 3466280, 1969; *Chem. Abstr*. **1970**, *72*, 66972.
3. Nakamura, T.; Takagiand, M.; Ueda, N. Indole Compound and Medicinal Use Thereof. *Patent* WO 2003037864, 2003; *Chem. Abstr*. **2003**, *138*, 368761.
4. Broadhurst, M.J.; Johnson, W.H.; Walter, D.S. Cyclic Hydrazine Derivatives as TNF-alpha Inhibitors. *Patent* WO 2000035885, 2000; *Chem. Abstr*. **2000**, *133*, 58802.
5. Konnert, L.; Lamaty, F.; Martinez, J.; Colacino, E. Recent Advances in the Synthesis of Hydantoins: The State of the Art of a Valuable Scaffold. *Chem. Rev.* **2017**, *117*, 13757–13809.
6. Cho, S.; Kim, S.-H.; Shin, D. Recent applications of hydantoin and thiohydantoin in medicinal chemistry. *Eur. J. Med. Chem*. **2019**, *164*, 517–545.
7. Yankov, A.N.; Shutalev, A.D. A new straightforward approach to 3-(arylideneamino)hydantoins. *Chem. Het. Comp.* **2020**, *56*, 1535–1541 and references herein.
8. Riches, A.G.; Cablewski, T.; Glattauer, V.; Thissen, H.; Meagher, L. Scalable synthesis of an integrin-binding peptide mimetic for biomedical applications. *Tetrahedron* **2012**, *68*, 9448–9455.
9. Schlögl, K. Über β-Isocyanat-fettsäureester und einige ihrer Reaktionsprodukte. Harnstoffe—Dihydrouracile-β-Alanin-peptide. *Monatsh. Chem.* **1958**, *89*, 61–73.
10. Wu, S.; Janusz, J.M.; Sheffer, J.B. An efficient one-pot synthesis of 3-aminohydantoin and 3-aminodihydrouracil derivatives. *Tetrahedron Lett.* **2000**, *41*, 1159–1163.
11. Wu, S.; Janusz, J.M. Solid-phase synthesis of 3-aminohydantoin, dihydrouracil, thiohydantoin and dihydrothiouracil derivatives. *Tetrahedron Lett.* **2000**, *41*, 1165–1169.
12. Vincent-Rocan, J.-F.; Clavette, C.; Leckett, K.; Beauchemin, A.M. A Cascade Synthesis of Aminohydantoins Using In Situ-Generated *N*-Substituted Isocyanates. *Chem.–Eur. J.* **2015**, *21*, 3886–3890.
13. Fesenko, A.A.; Banschikov, P.E.; Shutalev, A.D. New synthesis of β-(4-semicarbazido)carboxylic acid-based peptidomimetics and 3-amino-5,6-dihydrouracils via an amidoalkylation protocol. *Org. Biomol. Chem*. **2025**, 23, 8301–8324.
14. Calzolari, A.; Conti, F.; Franconi, C. Nuclear magnetic resonance studies of the hindered internal rotation of *NN*-disubstituted amides. Part VII. Solvent effects on the *N*-methyl resonance shifts and activation parameters. *J. Chem. Soc. B* 1970, 555–562.
15. Phillips, A.M.F.; Pombeiro, A.J.L. Atropselective Organocatalytic Synthesis of Chiral Compounds Containing Nitrogen along the Axis of Chirality. *Symmetry* **2023**, *15*, 1261.
16. Mei, G.-J.; Wong, J.J.; Zheng, W.; Nangia, A.A.; Houk, K.N.; Lu, Y. Rational design and atroposelective synthesis of N–N axially chiral compounds. *Chem* **2021**, *7*, 2743–2757.