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*Mendeleev Commun.*, 2015, **25**, 221–223
Mendeleev Communications

# Chlorination of 5-nitro-6-methyluracil and its *N*(1),*N*(3)-dimethyl analogue with molecular chlorine

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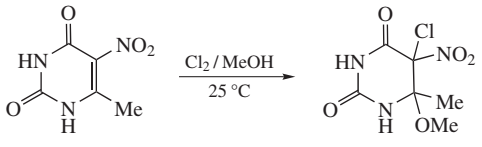
DOI: 10.1016/j.mencom.2015.05.022

**The chlorination of 6-methyl-5-nitrouracil with chlorine in methanol results in a two-component mixture of 5-chloro-6-methyl-6-methoxy-5-nitro-5,6-dihydrouracils, while the chlorination of 5-nitro-1,3,6-trimethyluracil under similar conditions gives a mixture of 5-chloro-6-hydroxy-5-nitro-1,3,6-trimethyl-5,6-dihydrouracils. The structures of the chlorination products were suggested based on quantum-chemical calculations.**

The functionalization of pyrimidine derivatives is promising for the development of efficient pharmaceuticals.[1–7] Of interest are halogenated pyrimidine bases, including uracil, which manifest a broad spectrum of pharmacological activity and are convenient synthons for the syntheses of bioactive compounds.[1–9]

The chlorination of 6-methyluracil and its 5-halogen derivatives was studied previously.[10,11] The chlorination of 6-methyluracil and 5-iodo-, 5-bromo- or 5-chloro-6-methyluracil with gaseous chlorine gave 5,5-dichloro-6-hydroxy-6-methyl-5,6-dihydrouracil. In this work, we studied the chlorination of the 5-nitro derivatives of 6-methyluracil and 1,3,6-trimethyluracil with molecular chlorine.

The chlorination of 6-methyl-5-nitrouracil **1** was carried out in $H_2O$, $CHCl_3$, AcOH and MeOH solvents at room temperature. However, a stereoisomeric two-component mixture of 5-chloro-6-methoxy-6-methyl-5-nitro-5,6-dihydrouracils **2** was isolated in 83% yield only in the case of methanol (Scheme 1).†



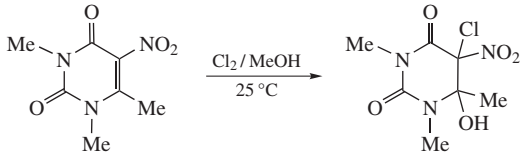

**1** **2** (83%)

**Scheme 1**

† *5-Chloro-6-methoxy-6-methyl-5-nitro-5,6-dihydrouracils* **2a**,**b**. Humid $Cl_2$ was passed through a solution of 6-methyl-5-nitrouracil **1** (0.25 g, 1.5 mmol) in MeOH (5 ml) for 30 min. The resulting yellowish green mixture was stirred for 2 h at room temperature. The solution was evaporated to dryness *in vacuo*. The precipitate was washed with $CH_2Cl_2$ and reprecipitated from EtOH. The light yellow powder was a mixture of compounds **2a** and **2b**. Yield, 0.29 g (83%). $^1$H NMR (DMSO-$d_6$) $\delta$: 1.59 (s, 3H, Me), 3.21 (s, 3H, OMe), 9.16 (s, 1H, HN$^1$), 11.18 (s, 1H, HN$^3$). $^{13}$C NMR (DMSO-$d_6$) $\delta$: 16.20 and 16.26 (Me), 49.49 (OMe), 106.59 (C$^5$), 107.33 (C$^6$), 150.42 (C$^2$), 159.00 and 159.18 (C$^4$). MS (ESI), *m*/*z*: 175 $[M-NO_2-CH_4]^-$ (100), 177 (27).

*5-Chloro-6-hydroxy-5-nitro-1,3,6-trimethyl-5,6-dihydrouracils* **4a**,**b** were synthesized analogously from 1,3,6-trimethyl-5-nitrouracil **3** (0.20 g, 1.0 mmol). The yellow powder was a mixture of compounds **4a** and **4b**. Yield, 0.13 g (50%). $^1$H NMR (DMSO-$d_6$) $\delta$: 1.62 and 1.71 (s, 3H, Me), 2.95 and 2.97, 3.18 and 3.21 (s, 3H each, MeN$^1$ and MeN$^3$), 3.60 (br. s, 1H, OH). $^{13}$C NMR (DMSO-$d_6$) $\delta$: 20.18 and 21.04 (Me), 27.81, 28.45 and 28.87 (MeN$^1$ and MeN$^3$), 84.61 and 85.41 (C$^6$), 102.70 and 103.58 (C$^5$), 149.71 and 150.82 (C$^2$), 157.71 and 158.10 (C$^4$). MS (ESI), *m*/*z*: 250 $[M-H]^-$ (100), 252 (34).

The chlorination of 5-nitro-1,3,6-trimethyluracil **3**, which was obtained by the methylation of 6-methyl-5-nitrouracil **1**,[12] with molecular chlorine in methanol afforded a mixture of 5-chloro-6-hydroxy-5-nitro-1,3,6-trimethyl-5,6-dihydrouracil stereoisomers **4** (Scheme 2).†

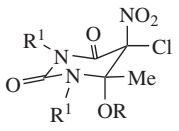



**3** **4** (50%)

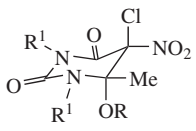
**Scheme 2**

Theoretical DFT calculations for the isomers of **2a**–**d** and **4a**–**d** showed that the dihydrouracil ring adopts a conformation close to twist or half-chair and the N$^1$–C$^4$ atoms lie in a plane (a deviation from planarity is about 11°). The C–$NO_2$ bond (1.55–1.57 Å) is much shorter than the C–Cl bond (1.77–1.79 Å); hence, it can make a larger contribution to the conformation effect. However, this contribution has almost no significance in the test compounds because they do not involve 1,3-diaxial interactions: there are no methyl groups at the N$^1$ and N$^3$ atoms in uracil **2**, while the methyl groups in **4** are arranged in the plane N$^1$–C$^4$ of the dihydrouracil ring.

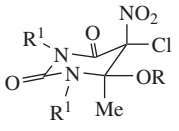
On the other hand, the dipole of the C–$NO_2$ bond (3.46 D in $MeNO_2$)[13] considerably exceeds the dipole of the C–Cl bond (1.87 D in MeCl),[13] which can result in a stronger repulsion from



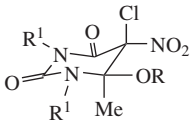

**2a** R = Me, R$^1$ = H
**4a** R = H, R$^1$ = Me




**2b** R = Me, R$^1$ = H
**4b** R = H, R$^1$ = Me




**2c** R = Me, R$^1$ = H
**4c** R = H, R$^1$ = Me




**2d** R = Me, R$^1$ = H
**4d** R = H, R$^1$ = Me

the dipole of the $C^4$=O group in the case of the C–$NO_2$ bond. Considerable steric interactions can occur if there is a Me group at the $N^1$ atom and two substituents at the $C^5$ and $C^6$ atoms.[14]

Theoretically, four stereoisomers (**a**–**d**) are possible for compounds **2** and **4**. The thermodynamic preferability of the formation of these isomers was studied using DFT.

All calculations were carried out using the Gaussian-09 program, Revision C1.[15] The results were visualized using the ChemCraft program, Version 1.6.[16] Initially, the structures of **2a**–**d** and **4a**–**d** were optimized in B3LYP/6-311G(d,p) approximation.[17–20] It was determined by the calculations of vibration frequencies that all the structures found correspond to minima on the potential energy surface. Furthermore, the zero vibration energies of the molecules and thermal corrections to the thermodynamic functions at 298 K were calculated. After that, the energies of the stereoisomers were refined by the B3LYP/6-311+G(d,p) method, and the solvation energy in DMSO or methanol was calculated in the same approximation using the IEFPCM polarized continuum method.[21] The relative Gibbs energies for compounds **2a**–**d** and **4a**–**d** are given in Table 1. An analysis of the calculated energies and electron density distributions in the compounds made it possible to distinguish three main factors determining the conformational potentials of compounds **2** and **4**: (1) anomeric stabilization of conformers with an axially oriented OR substituent at the $C^6$ atom (R = Me in **2** and H in **4**); (2) competitive *a*–*e* orientation of polar substituents ($NO_2$ and Cl) at the 5-position of the dihydrouracil ring; (3) intramolecular hydrogen bond in **4** between the hydroxy and nitro groups.

(1) The common feature in the structures of the test conformers is that the states with an axially oriented substituent (OMe in **2** and OH in the **4**:$H_2O$ 1:1 complexes) are more energetically favorable (Table 1). This effect was studied for the model compound 5,6-dihydro-6-methoxyuracil, where factors (2) and (3) are not in effect. As shown by the calculations of the energies of various conformers and analysis of electron density based on the natural bond orbitals method (NBO),[22] the observed regularity is a manifestation of the anomeric effect[23] caused by the stabilizing non-valent interaction of the unshared electron pair of the $N^1$ atom and the antibonding σ* orbital of the $C^6$–O bond, $n(N^1) \rightarrow \sigma^*(C^6–O)$ (Figure 1). The reverse interaction $n(O) \rightarrow \sigma^*(C^6–N^1)$ is also in effect. It results in a thermodynamically favorable *syn*-clinal orientation of the Me group in the methoxy substituent and the $N^1$ atom as is the case of compounds **2a**,**b**. The energies of nonvalent stabilization for various conformers of 5,6-dihydro-6-methoxyuracil are presented in Table 2. The population of the most stable structure (*a* OMe, +*sc* Me) is 84%, and the total population of the three conformers with an axially oriented methoxy group is as high as 98%.

**Table 1** Relative standard Gibbs energies for isomers **2a**–**d** and **4a**–**d** based on the results of DFT calculations.

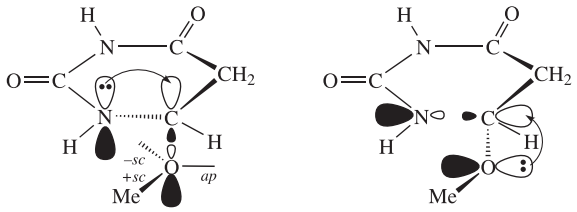
| Conformer | Conformation[a] | | $\Delta G^{0\,b}$/ kcal mol$^{-1}$ | Population (%) |
|---|---|---|---|---|
| | OR | $NO_2$ | | |
| | R = Me | | | |
| **2a** | *a* | *a* | 0.01 | 49 |
| **2b** | *a* | *e* | 0.00 | 51 |
| **2c** | *e* | *a* | 3.59 | 0 |
| **2d** | *e* | *e* | 5.49 | 0 |
| | R = H | | | |
| **4a** | *a* | *a* | 0.00 (0.00)[c] | 40 (50) |
| **4b** | *a* | *e* | 0.33 (0.22) | 23 (34) |
| **4c** | *e* | *a* | 0.05 (3.32) | 37 (0) |
| **4d** | *e* | *e* | 3.95 (0.68) | 0 (16) |

[a] *a* and *e* refer to the axial and equatorial orientations of substituents relative to the ring plane, respectively. [b] Relative Gibbs energy of the isomer (zero corresponds to the most stable structure) calculated with consideration for the effect of DMSO as the solvent. [c] The data in parentheses correspond to the **4**:$H_2O$ complexes (1:1), where the formation of an intramolecular hydrogen bond is impossible.

**Table 2** Nonvalent stabilization energies of 5,6-dihydro-6-methoxyuracil conformers based on the results of NBO analysis of electron density (kcal mol$^{-1}$) and their population values calculated from the absolute Gibbs energies of the conformers.

| | OMe orientation[a] | Me[b] | | |
|---|---|---|---|---|
| | | +*sc* | –*sc* | *ap* |
| $n(N^1) \rightarrow \sigma^*(C^6–O)$ | *a* | 15.17 | 14.08 | 13.51 |
| $n(O) \rightarrow \sigma^*(C^6–N^1)$ | *a* | 10.89 | 10.65 | 1.09 |
| Population (%) | *a* | 84 | 2 | 12 |
| $n(N^1) \rightarrow \sigma^*(C^6–O)$ | *e* | 3.72 | 3.10 | 3.19 |
| $n(O) \rightarrow \sigma^*(C^6–N^1)$ | *e* | 11.90 | 10.38 | 1.66 |
| Population (%) | *e* | 1 | 0 | 1 |

[a] *a* and *e* refer to the axial and equatorial orientations of the substituent relative to the ring plane, respectively. [b] *sc* is *syn*-clinal orientation, *ap* is *anti*-periplanar orientation of the methyl group with respect to the $N^1$ atom.




$n(N^1) \rightarrow \sigma^*(C^6–O)$ $n(O) \rightarrow \sigma^*(C^6–N^1)$

**Figure 1** Anomeric effect in 5,6-dihydro-6-methoxyuracil.

(2) In model 5,6-dihydrouracils and 5,6-dihydro-6-methyluracils containing an $NO_2$ (or Cl) substituent at the 5-position, both substituents prefer an axial orientation with respect to the plane of the dihydropyrimidinedione ring. The energy difference of *a* and *e* conformers is 0.5–1.5 kcal mol$^{-1}$ for both substituents; this is likely due to repulsion between the dipoles of the carbonyl $C^4$=O and $C^5$–$NO_2$ ($C^5$–Cl) groups. If both electronegative substituents are present at the 5-position, both possible stereoisomers have nearly the same energies (⩽0.06 kcal mol$^{-1}$) and hence equal populations. These results totally agree with the data for uracil **2** (Table 1), in which only stabilization effects of types (1) and (2) are manifested. Model calculations allowed us to assume that the doubling of the NMR signals recorded for compound **2** is due to the simultaneous presence of comparable amounts of conformers **2a** and **2b** in the test solution (Table 1).

(3) The presence of a hydroxy group in uracil **4** allows its isomers to be stabilized by the formation of an intramolecular hydrogen bond (IHB) OH···ONO (Figure 2). The results of our calculations indicate that an IHB is formed in all the isomers except for **4a**, but the strength of this bond is likely to vary considerably. Table 3 lists the calculated values that characterize the IHB strength, in particular, the hydrogen bond length, the plane angle OH···O that tends to 180° in the strongest complexes, as well as the shift in the characteristic vibration frequency of the O–H bond in comparison with the vibration frequency of the free hydroxyl (in isomer **4a**). All the characteristics show that the strongest IHB is formed in isomer **4c**; hence, the free Gibbs energy of **4c** decreases to nearly the same value as the $G^0$ of the most stable isomer **4a** (Table 1). In the DMSO or methanol solutions, intramolecular bonding efficiently competes with IHB formation since the solvent molecules contain oxygen atoms that are electron density donors. In order to simulate this possibility, we calculated the optimum structures of the complexes of isomers **4**

**Table 3** Formation of intramolecular hydrogen bonds in **4** according to B3LYP/6-311G(d,p) calculation data.

| Orientation of $NO_2$ and OH | Conformer | O–H···ONO[a]/Å | ∠O–H···O | $\Delta\nu_{OH}$[a]/cm$^{-1}$ |
|---|---|---|---|---|
| *e–a* | **4b** | 1.897 | 135.5 | 91 |
| *a–e* | **4c** | 1.880 | 141.0 | 134 |
| *e–e* | **4d** | 2.120 | 135.6 | 54 |

[a] $\Delta\nu_{OH} = \nu_{OH}$(**4a**) – $\nu_{OH}$(**4b**,**c**,**d**), calculation without consideration for the solvent and without scaling the vibration frequency values. Formation of an OH···ONO intramolecular hydrogen bond is not possible in isomer **4a**.

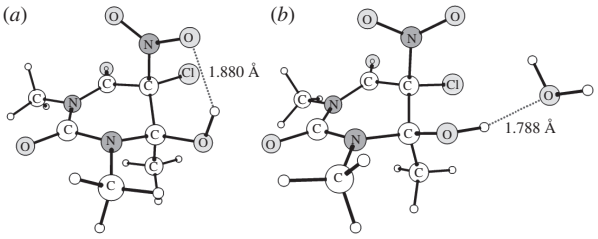



**Figure 2** Equilibrium structures of **4c** stabilized by an (*a*) intramolecular or (*b*) intermolecular hydrogen bond. The calculation was carried out in B3LYP/6-311G(d,p) approximation.

with one water molecule (Figure 2). In all the complexes, the H atom of the hydroxy group was an electron density acceptor, whereas the O atom of a water molecule was a donor. The relative Gibbs energies of these complexes and the equilibrium populations of compounds **4a–d** are given in Table 1. In the model that better approximates real conditions, a considerable redistribution of the relative stability of isomers **4** occurs. A decrease in the role of factor (3), *i.e.*, IHB, results in the predomination of structures **4a** and **4b**, similarly to that described above for uracil **2**. Therefore, we assume that the signal doubling in the $^{13}$C and $^{1}$H NMR spectra of **4** is due to the coexistence of isomers with a hydroxy group axially oriented with respect to the ring plane in solution. This is indirectly confirmed by the fact that, according to our theoretical calculations, as an OH group is replaced with OMe, the overall population of isomers **4a′** and **4b′** reaches 96% at a ratio of ~2.4:1 between them.

All calculations were carried out at the Center for Collective Use in the Ufa Institute of Chemistry of the Russian Academy of Sciences. This study was supported by the Division of Chemistry and Materials Science of the Russian Academy of Sciences for 2014 (programme for fundamental studies OKh-01) and the RF President Council on Grants (State Support Program for Leading Scientific Schools of the Russian Federation, grant no. NSh-7014.2012.3).

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*Received: 7th October 2014; Com. 14/4480*