JOC Article

Ab Initio Study of the (5*R*)- and (5*S*)-TT Pyrimidine h^5(6−4) Pyrimidone Photoproducts. Implications on the Design of New Biologically Relevant Analogues

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A computational study of a series of N_1- and/or C_6-alkyl-5,6-dihydrothymine diastereomers at theory levels up to MP4(SDTQ)/6-31G*//HF/6-31G* and MP2/6-311G**//HF/6-31G* has demonstrated the respective importance of the substituents at positions 1, 5, and 6 on the energetically favored conformation of each isomer. Results obtained both in the gas and condensed phase indicate that unsubstitution of the N_1-position favors a half-chair conformation with the C_5 -and C_6-substituents in the equatorial position. On the other hand, in the case of the (6*S*)-1,6-dimethyl-5,6-dihydrothymine, the C_6-substituent adopts the axial position to minimize its van der Waals interactions with the N_1-substituent. Furthermore, if the configuration at the C_5-dihydrothymine position has no resultant influence on the total molecular free energy, when a pyrimidone substituent is introduced at the dihydrothymine C_6-position, additional repulsive forces between the C_5- and C_6-substituents make the diaxially substituted half-chair conformation the most energetically favorable one. These results indicate that the observed C_6-axially substituted conformation of the thymine-thymine pyrimidine h^5(6−4) pyrimidone photoproducts is not necessarily induced by the macrocyclic structure. They also nicely explain the formation mechanism of these photoproduct derivatives, and allow the prediction of the conformation of new analogues.

Introduction

6-Alkyl-5,6-dihydrothymines constitute a class of biologically highly important DNA damaged products that are generated by γ-radiation of thymine[1a] or thymidine[1b] or encountered in the UV-generated pyrimidine (6−4) pyrimidone photoproducts [(6−4)PPs].[2] (6−4)PPs resulting from a Paterno−Büchi reaction between two adjacent pyrimidine bases represent one of the most common and also one of the major mutagenic UV-induced DNA damage.[2,3] These compounds are also strongly suspected to be involved in sunlight-induced skin cancer.[4] For these reasons, their bypass by DNA polymerases during replication [translesion synthesis (TLS)] is currently receiving considerable attention. Even if research in this field is being stimulated by the recent discovery of new DNA polymerases,[5] a better understanding of the (6−4)PP chemistry is still necessary to intimately comprehend the rules governing their structure−mutagenicity relationships. This could be efficiently achieved by studying well-designed (6−4)PP analogues that would unambiguously settle the exact importance of the nature and stereochemistry of every single (6−4)PP-substituent in the biological processes.

Considering that the evaluation of the influence of the 5′-end-pyrimidine C_5-substituent and of its stereochemistry during TLS would be facilitated if variously C_5-substituted analogues were available, we recently reported the synthesis of two (6*R*)-(6−4)PP-dinucleotide analogues (**1a**,**b**), epimers at the 5,6-dihydropyrimidine 5-position.[6] These compounds, prepared to be later incorporated into oligonucleotides, were designed to be the dinucleotide analogues of either the thymine-thymine

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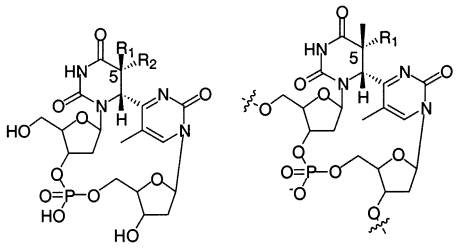
or thymine-5-methylcytosine (6−4) photoproduct (**2a** or **2b**), lacking respectively the hydroxyl or the amino group substituting the dihydropyrimidine quaternary 5-position, to probe the contribution of these groups on mutagenicity.



1a : R_1=CH_3, R_2=H **2a :** R_1=OH

1b : R_1=H, R_2=CH_3 **2b :** R_1=NH_2

The principle of using analogues such as **1a** and **1b** in biological studies implies that they are supposed to induce DNA structural perturbations similar to those produced by the natural (6−4)PPs. Interestingly, we were able to deduce from NMR data that in solution, the 5,6-dihydropyrimidine moiety of **1a** and **1b** adopts a half-chair conformation in which the C_5- and C_6-atoms are respectively above and below the N_1-C_4 mean plane,[6] as calculated[7] and recently observed[8] for the (6−4) adducts of TpT. Since in **1a** and **1b** the C_6-atom is *R*-configured, the observed half-chair conformation implies that in both cases the C_6-substituent is axially oriented. Additionally, if in **1b** the C_5-methyl group adopts the equatorial orientation, it occupies the axial one in **1a**, meaning that this latter compound is 5,6-diaxially substituted. This substitution pattern is unusual, particularly considering that **1a** has been obtained, in quantitative yield, by alkaline treatment of the C_5-Me_{eq}-C_6-Pyr_{ax} derivative **1b**. Assuming that the C_5-epimerization reaction of **1b** proceeded through an enol intermediate, we proposed the *vic*-diaxial **1a** to be the thermodynamically most stable species.[6]

In the present paper, we have studied the energy difference between the two (6*R*) compounds **1a** and **1b** using ab initio calculations. Then, to get insight into the parameters governing the preferred 5,6-diaxial substitution pattern, the possible relationships between the N_1- and/or C_6-5,6-dihydrothymine substituent(s) and the configuration at C_5 are delineated. For this, we have performed calculations on 5,6-dihydrothymines **3**, **4**, and their N_1- and/or C_6-substituted derivatives **5**−**10′** (Chart 1). To confirm the emerging rules, we have also studied **11**−**14′**, which more closely mimic the nucleobase portion of **1a** and **1b**. Compounds **15-16′** were finally examined to determine the influence of the size of the C_6-substituent on the C_5-configuration and to extend the rules to other (6−4)PP analogues.

Computational Methods

Gas Phase. Geometries were fully optimized at the Hartee−Fock (HF) level using the 6-31G (for **1a**,**b**) and 6-31G* (for **3**−**16′**) basis sets.[9,10] Single-point energy calculations were carried out on all optimized molecules using theory levels up to MP4(SDTQ)/6-31G*//HF/6-31G* and MP2/6-311G**//HF/6-31G*.[10,11] Frequency analyses were performed using the 6-31G (for **1a**,**b**) and 6-31G* (for **3**−**16′**) theory levels to verify the nature of the minima located during the geometry optimization, as well as to obtain zero-point energy (ZPE), thermal (298.15 K), and entropic corrections. Enthalpies were evaluated from the energies computed at the MP2 and MP4 Møller−Plesset levels,[11] corrected for ZPE (scaling factor 0.89)[12] and thermal effects. Free energy differences between the isomers were determined according to $\Delta G = \Delta H - T\Delta S$. This protocol is summarized in the Supporting Information and was performed using standard procedures implemented in GAMESS-US and PC-GAMESS.[13,14]

Condensed Phase. Calculations of free energy differences in methanol solution for isomers **3**−**10′** were performed according to the thermodynamic cycle presented in the Supporting Information. Solvation free energies were determined using the MP2/6-311G**//HF/6-31G* COSMO (Conductor-like Screening Model) algorithm implemented in GAMES-US where the surrounding medium is modeled as a conductor.[15] Default COSMO parameters and a dielectric constant of 33 were used during all the simulations.

Results and Discussion

Gas Phase. The free energy (ΔG), enthalpy (ΔH), and entropy (ΔS) differences of the studied molecules are shown in Table 1. Calculations at the MP2/6-31G*//HF/6-31G level confirmed our previous prediction[6] for we found the *vic*-axial−equatorial isomer **1b** to be 1.1 kcal mol^{-1} higher in energy than the *vic*-diaxial **1a**. In an attempt to explain this result, we then performed further calculations on a series of 5,6-dihydropyrimidines, using 5,6-dihydrothymine enantiomers **3** and **4** as an initial model. X-ray diffraction data,[16] together with IR- and NMR-based conformational analyses,[17] have indicated the 5,6-dihydrothymine half-chair conformation, in which the methyl group is in the equatorial orientation, to be the most stable. Because previous calculations performed using Hückel theory or at the MP2/6-31G*//HF/6-31G theory level have indicated only a very minute energy difference between **3** and **4**,[18,19] we decided to verify these calculations using larger basis sets.

In the gas phase, at the MP4(SDTQ)/6-31G*//HF/6-31G* as well as MP2/6-311G**//HF/6-31G* theory levels, we also found the lowest free energy isomer to be

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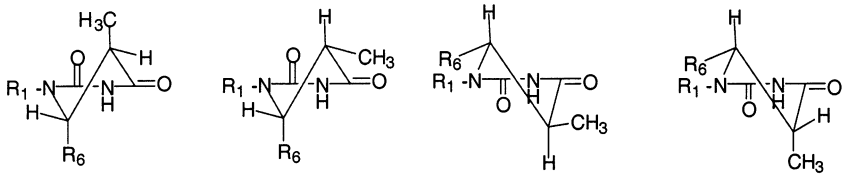
CHART 1. Structure of Compounds 3-16′



$R_1 = R_6 = H$

3 **4**

$R_1 = CH_3$, $R_6 = H$

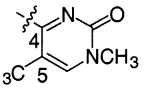
5 **6**

$R_1 = H$, $R_6 = CH_3$

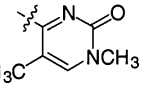
7 **8** **7'** **8'**

$R_1 = R_6 = CH_3$

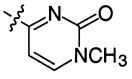
9 **10** **9'** **10'**

$R_1 = CH_3$, $R_6 =$ 

11 **12** **11'** **12'**

$R_1 = H$, $R_6 =$ 

13 **14** **13'** **14'**

$R_1 = CH_3$, $R_6 =$ 

15 **16** **15'** **16'**

Underlining indicates the most stable structures

the equatorial form **4**, whose free energy barrier with the axial form was found to be 0.90 and 0.72 kcal mol^{-1}, respectively (vs 0.45 to 0.74 kcal mol^{-1} at other theory levels).[19] Comparison between the structural X-ray parameters reported for **4**[16] and those obtained from our calculations (Table 2) indicated the heavy-atom root-mean-square deviation to be 0.0680 Å and consequently confirmed the accuracy of our calculation.

We then studied how the 5,6-dihydrothymine N_1-substitution could affect the C_5-methyl preferred orientation. For this, we compared the free energy of the two half-chair conformations of the N_1-methyl-5,6-dihydrothymine **5** and **6**. At the MP4(SDTQ)/6-31G*//HF/6-31G* and MP2/6-311G**//HF/6-31G* theory levels, the free energy barrier between the slightly disfavored axially substituted **5** and the equatorially substituted **6** was found to be 0.84 and 0.62 kcal mol^{-1}, respectively, almost the same values as found for **3** and **4**. This observation clearly established that, in the absence of a C_6-substituent, the N_1-substitution does not influence the energy difference between the two isomers. Indeed, the preferred equatorial C_5-methyl orientation is, as in the case of **6** and **4**, only due to the removal of an unfavorable gauche effect occurring in **5** or **3** between the axial C_5-methyl and N_1 and N_3 atoms in the 5,6-dihydrothymine. In this paper, such gauche interactions will be termed "cycle" gauche effects (Scheme 1). Similar conclusions have already been reported on 3-pentanone, where the lowest conformer is the rotamer in which the methyl group is eclipsed with the carbonyl group, this conformation allowing the two alkyl groups to be anti rather than gauche.[20]

TABLE 1. Internal Energy Differences (Δ*E*, kcal mol⁻¹), Enthalpy Differences (Δ*H*, kcal mol⁻¹), Entropy Differences (−*TΔS*, kcal mol⁻¹), and Free Energy Differences (Δ*G*, kcal mol⁻¹) of 1−16′ at 298.15 K in the Gas Phase

	Δ*E*		Δ*H*		−*TΔS*	Δ*G*	
1a	0.00[a]		0.00[a]		0.00	0.00[a]	
1b	0.84[a]		0.83[a]		0.27	1.10[a]	
3	0.62[b]	0.80[c]	0.71[b]	0.89[c]	0.01	0.72[b]	0.90[c]
4	0.00[b]	0.00[c]	0.00[b]	0.00[c]	0.00	0.00[b]	0.00[c]
5	0.52[b]	0.74[c]	0.61[b]	0.83[c]	0.01	0.62[b]	0.84[c]
6	0.00[b]	0.00[c]	0.00[b]	0.00[c]	0.00	0.00[b]	0.00[c]
7	0.55[b]	0.57[c]	0.58[b]	0.60[c]	0.04	0.61[b]	0.64[c]
7′	0.00[b]	0.00[c]	0.00[b]	0.00[c]	0.00	0.00[b]	0.00[c]
8	0.40[b]	0.42[c]	0.41[b]	0.43[c]	0.20	0.61[b]	0.63[c]
8′	0.70[b]	0.99[c]	0.79[b]	1.08[c]	0.14	0.94[b]	1.23[c]
9	0.06[b]	0.08[c]	0.08[b]	0.10[c]	−0.18	−0.10[b]	−0.08[c]
9′	1.78[b]	1.86[c]	1.91[b]	2.00[c]	0.19	2.10[b]	2.19[c]
10	0.00[b]	0.00[c]	0.00[b]	0.00[c]	0.00	0.00[b]	0.00[c]
10′	1.95[b]	2.33[c]	2.14[b]	2.53[c]	0.33	2.47[b]	2.86[c]
11	0.00[b]	0.00[d]	0.00[b]	0.00[d]	0.00	0.00[b]	0.00[d]
11′	1.52[b]	1.94[d]	1.51[b]	1.93[d]	−0.35	1.15[b]	1.58[d]
12	0.43[b]	0.47[d]	0.40[b]	0.44[d]	0.06	0.46[b]	0.50[d]
12′	3.62[b]	4.36[d]	3.72[b]	4.46[d]	−0.09	3.63[b]	4.37[d]
13	0.85[b]	0.50[d]	0.92[b]	0.57[d]	0.47	1.39[b]	1.04[d]
13′	1.52[b]	1.47[d]	0.83[b]	0.78[d]	1.58	2.41[b]	2.36[d]
14	1.22[b]	0.90[d]	1.25[b]	0.92[d]	0.27	1.51[b]	1.20[d]
14′	0.00[b]	0.00[d]	0.00[b]	0.00[d]	0.00	0.00[b]	0.00[d]
15	0.00[b]	0.00[d]	0.00[b]	0.00[d]	0.00	0.00[b]	0.00[d]
15′	1.20[b]	1.75[d]	1.17[b]	1.72[d]	−0.15	1.02[b]	1.57[d]
16	0.01[b]	0.25[d]	−0.02[b]	0.22[d]	−0.01	−0.03[b]	0.21[d]
16′	3.31[b]	4.08[d]	3.38[b]	4.16[d]	−0.10	3.28[b]	4.05[d]

[a] MP2/6-31G*//HF/6-31G. [b] MP2/6-311G**//HF/6-31G*. [c] MP4(SDTQ)/6-31G*//HF/6-31G*. [d] MP4(SDQ)/6-31G*//HF/6-31G* theory level.

Next, we concentrated our study on the free energy of 6-substituted-5,6-dihydrothymines and, in analogy with **1**, chose (6*S*)-methyl derivatives (**7**−**8′**). The internal energy of the four possible (6*S*)-isomers was calculated and the lowest energy was found for the diequatorial isomer **7′** (Table 1). Interestingly, molecules **7** and **8** (C_6-Me_{ax}) were found to have almost identical free energies at both ab initio theory levels reported. Structure **8′** (C_6-Me_{eq}) has the highest free energy, 0.94 (1.23) kcal mol⁻¹ higher compared to **7′**. Determination of these free energy differences turned out to be highly informative as they could be related to the number of unfavorable van der Waals interactions. Indeed, **7′** presents only one unfavorable gauche trans-diequatorial interaction (between the C_5 and C_6 methyls) whereas **7**, **8**, and **8′** display two unfavorable interactions (a "cycle" gauche and a gauche interaction for **8** and **8′** and two "cycle" gauche interactions for **7**). As structures **7**, **8**, and **8′** showed similar free energies, this demonstrated that the effects of "cycle" gauche and gauche interactions were of almost equal magnitude.

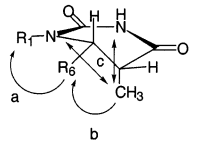
As for the unsubstituted 5,6-dihydrothymine series, we evaluated the influence of N_1-substitution of 6-substituted-5,6-dihydrothymines on their relative stability. The free energy of the four (6*S*)-1,6-dimethyl-5,6-dihydrothymines **9**−**10′** was calculated, and the isomers **9** and **10** were found to be of roughly equal, lower energy. In these two cases, the C_6-substituent occupies an axial position, the difference stemming from the C_5-methyl orientation. The similar free energy values for **9** and **10**, as observed for **7** and **8**, confirmed that the result of two "cycle" gauche interactions is equivalent to the effect of the sum of one "cycle" gauche and one gauche interaction. We attributed the energetic order observed in this series to the presence of the most unfavorable van der Waals interactions between the N_1- and C_6-substituents in the case of C_6-equatorial substitution, hence forcing the C_6-substituent to adopt an axial orientation to minimize repulsive steric interactions between the N_1- and C_6-substituents.

To confirm this latter hypothesis observed in the methyl series, we decided to evaluate derivatives in which position C_6 would be substituted by a larger group and, hence, for which this putative repulsive interaction would be more pronounced. To be closer to the (6*R*)-h⁵(6−4)PP-analogues, we examined the respective free energy of the four (6*R*)-1-methyl-6-(1,5-dimethylpyrimidone)-5,6-dihydrothymines (**11**−**12′**) and then compared the observed stability order to that of the four (6*R*)-6-(1,5-dimethylpyrimidone)-5,6-dihydrothymines **13**−**14′**. Once again, dramatic differences were observed between the N_1-H and

TABLE 2. Comparison between the X-ray[16] Structure of 4 (CSD Entry DHTHYM, Cambridge Data Bank) and Its Optimized Structure

	DHTHYM	HF/6-31G* basis set, gas phase
	bond length (Å)	
N1−C2	1.326	1.357
C2−O2	1.235	1.196
C2−N3	1.383	1.386
N3−C4	1.358	1.377
C4−O4	1.212	1.192
C4−C5	1.531	1.519
C5−C6	1.516	1.526
C5−C7	1.538	1.527
N1−C6	1.450	1.449
mean diff	0.016 (standard error = 0.012)	
	bond angles (deg)	
N1−C2−N3	116.6	114.4
N1−C2−O2	123.9	124.4
N1−C6−C5	108.5	109.5
C2−N3−C4	126.3	127.8
C2−N1−C6	122.1	121.4
N3−C4−C5	113.4	115.1
N3−C4−O4	121.1	121.0
C4−C5−C6	108.1	110.1
C4−C5−C7	110.3	111.4
C5−C4−O4	124.0	124.0
C6−C5−C7	110.5	112.8
mean diff	1.2 (standard error = 0.8)	

SCHEME 1. Representation of the Three Interactions Governing the N_1,C_6-Disubstituted-5,6-dihydrothymine-Preferred Structure



unfavorable interaction strength: a > b ~ c

a: interaction between N_1- and eq. C_6-substituents.

b: gauche interaction between the C_6-substituent and the C_5-Me group.

c: "cycle" gauche interaction between the axial Me goup and cyclic N_1 and N_3 atoms.

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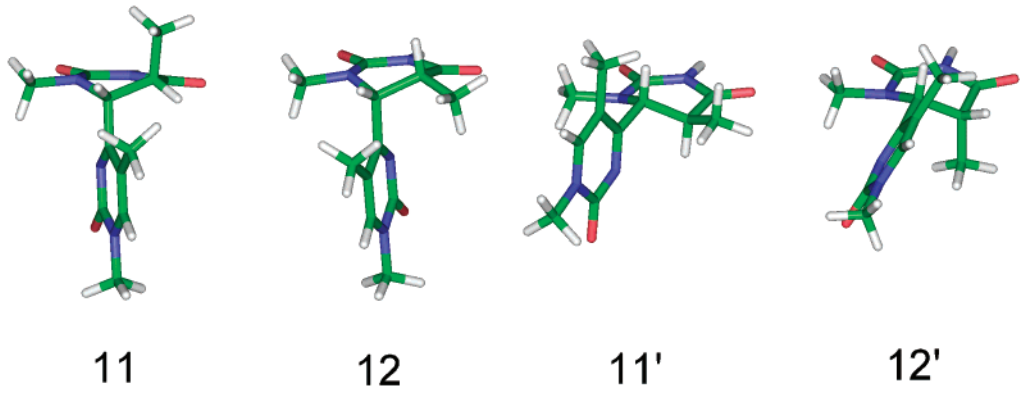


FIGURE 1. Calculated most stable conformation for isomers **11**−**12′**.

N_1-CH_3 series. In the N_1-unsubstituted series, the lowest energy isomer was found to be **14′** in which the C_6-substituent adopts an equatorial position, whereas in the N_1-methylated series, the most stable isomer was calculated to be the *vic*-diaxial **11**. The higher stability of **14′** compared to **13′** was first somehow surprising, considering that in the corresponding C_6-methylated series (**7**−**8′**) compound **8′** (C_5-Me_{ax}) had been found to be the less favored isomer. For **14′**, N_1-unsubstitution allows the C_6-substituting dimethylpyrimidone to adopt a less unstable conformation in which the gauche interaction between the C_5- and C_6-substituents is minimized. This was evidenced by measuring the torsion angle between atoms C_5 and C_4 of the pyrimidone and atoms C_6 and N_1 of the 5,6-dihydrothymine in **12′**, **14′**, and **16′** (vide infra). This torsion angle showed a homogeneous value of $-145 \pm 2°$ for the N_1-methyl derivatives **12′** and **16′** while its value for **14′** was −165°. Moreover, in the case of a 5,6-diequatorial substitution (**13′**), we evidenced an additional steric interaction between the C_5-methyl of the 5,6-dihydrothymine and the C_5-methyl of the 1,5-dimethylpyrimidone substituent. Such interaction disfavored isomer **13′** and also nicely explains the lower free energy of **13** compared to **14**. Having fully identified the two possible conflictual types of interaction (importance of the N_1-substitution on the C_6-orientation and importance of the C_6-substituent on the C_5-substituent orientation), we expected that in the N_1-CH_3 series (**11**−**12′**) the *vic*-diaxially disubstituted compound (**11**) should be the one of lowest energy followed by its C_5-epimer (**12**). Indeed, the calculations confirmed this, the most stable isomer being **11**, in which the C_5- and C_6-substituents are both axial, and the next stable isomer being C_5-Me_{eq}-C_6-Pyr_{ax} **12** (ΔG = 0.46 and 0.50 kcal mol^{-1}). This is explained by a molecular conformation reducing the unfavorable van der Waals interaction between the C_5-methyl of the 5,6-dihydrothymine and the C_5-methyl of the 1,5-dimethylpyrimidone (Figure 1). In the case of an equatorial C_6-substitution, diequatorial structure **11′** was found to be more stable than the C_5-Me_{ax}-C_6-Pyr_{eq} **12′** as found for **9′** and **10′**.

To fully establish the importance of the size of the C_6-substituent, we finally studied the four (6*R*)-1-methyl-6-(*N*-methylpyrimidone)-5,6-dihydrothymines **15**−**16′**. Replacing the 1,5-dimethylpyrimidone by a 1-methylpyrimidone confirmed the presence of the anticipated additional van der Waals interaction between the 5,6-dihydrothymine methyl group and the C_6-substituent. Indeed, **15** and **16** were found to be of almost equal free energy, as had been found for **9** and **10**, where the C_6-position was substituted by a methyl group.

TABLE 3. Solvation Free Energy Difference between Each Isomer ($\Delta\Delta G_{solv}$, kcal mol^{-1}) and Free Energy Difference (ΔG_{cp}, kcal mol^{-1}) of 3−10′ at 298.15 K in Methanol [Calculated Using the COSMO Algorithm (MP2/6-311G//HF/6-31G* Basis Set)]**

	$\Delta\Delta G_{solv}$	ΔG_{cp}
3	0.12	0.84
4	0.00	0.00
5	−0.19	0.43
6	0.00	0.00
7	0.14	0.75
7′	0.00	0.00
8	−0.01	0.60
8′	0.01	0.95
9	−0.02	−0.12
9′	0.95	3.05
10	0.00	0.00
10′	0.88	3.35

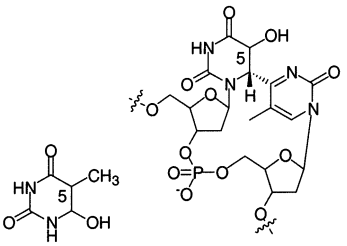
Condensed Phase. Although our calculations were carried out on molecules with only weakly polar groups, the small free energy differences observed in the gas phase (ΔG_{max}= 4.37 kcal mol^{-1}) incited us to study the possible influence of the solvent on the free energy of each series. We selected methanol for the study of the different isomers as the synthesis of **1a**,**b** had been achieved in this solvent.[6] Unfortunately, an error in the molecular cavity generation in the COSMO algorithm (GAMESS-US software) precluded the condensed phase calculations of larger isomers **1a**,**b** and **11**−**16′**. However, for compounds **3**−**10** similar free energy differences were obtained in methanol and in the gas phase, indicating the absence of a solvent effect (Table 3). This was further confirmed by a RMSD study of the structures optimized in gas and condensed phases. For the 12 molecules studied, a mean heavy-atom RMSD of 0.012 Å (standard error = 0.002) was observed compared with the corresponding structure minimized in the gas phase. The isomers of lowest energy were found to be identical in the two studies, indicating that the conclusions drawn in the gas phase are also relevant in solution.

From these results important conclusions can be drawn. First, our study clearly confirms our proposed mechanism for the formation of **1a**,**b** by showing that **1a** is indeed thermodynamically the most stable. Second, these results are of relevance since they demonstrate that

the half-chair conformation of the 5′-end of the h⁵(6−4)-PPs and the orientation of the C_5-methyl of 5,6-dihydrothymine is not influenced, or at least not totally influenced, by the deoxyribo-phosphate backbone, but is also a consequence of interactions between the N_1, C_6 and C_6, C_5 substituents. Consequently, our study constitutes a first step toward simple rules assisting the design of stereoselectively correctly substituted new 1,6-disubstituted-5,6-dihydrothymine photoproduct analogues.

Rules based on unfavorable "cycle" gauche and gauche interactions can be clearly expressed for 5,6-dihydrothymine derivatives: (i) The interaction between N_1- and C_6-substituents (interaction *a*, Scheme 1) is the major one. (ii) The strength of the gauche interaction between the C_6-substituent and the C_5-methyl group (interaction *b*, Scheme 1) depends on the nature of the C_6-substituent. In the case of a C_6-methyl group, the corresponding gauche interaction and the "cycle" gauche interaction (interaction *c*, Scheme 1) are of equal importance. On the other hand, when the size of the C_6-substituent increases (1,5-dimethylpyrimidone) the gauche interaction becomes predominant. In summary, the N_1-substituent of the 5,6-dihydrothymine is the driving force for the general molecular conformation and is responsible for the axial orientation of the C_6-substituent and, hence, for the axial C_5-methyl energetically most favored configuration.

These rules have been established in the case of alkyl substituents. Their extension to OH-substituted derivatives which are part of other biologically relevant series such as the thymine photohydrates (**17**) or the hydrolyzed product of the cytosine-thymine (6−4) photoproduct (**18**) requires additional calculations. Such data should allow the identification of the most stable isomer of **18** whose C_5-atom is prone to undergo isomerization.[21] This information would be critical to studying the role of the methyl group substituting the C_5-5,6-dihydrothymine of the TT (6−4)PP atom during TLS.



17 **18**

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Supporting Information Available: Single-point energies of the studied structures and schematic representation of the theory used for the calculation of the energies in the condensed and gas phases; gas-phase thermochemical data for **1a**,**b** and **3**−**16′**. This material is available free of charge via the Internet at http://pubs.acs.org.

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