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A theoretical study on cytosine tautomers in aqueous media by using continuum models

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Abstract

B3LYP/6-31++G** and MP2/6-31++G** calculations have been carried out to study six tautomers of the nucleic acid base cytosine in aqueous media. Solvent effects have been analyzed using the self-consistent reaction field theory with two continuum methods. Relative stabilities and optimized geometries have been calculated for the tautomers and compared with experimental data. The present results show the importance of electrostatic solvent effects in determining observable properties of the cytosine tautomers. The amino-oxo form (C1) is the most abundant tautomer in aqueous media while the other amino-oxo form (C4) is the most energetically favored when solvent effects are included. These results can be justified by the larger values of the dipole moments for both C1 and C4 tautomers. Theoretical and experimental results of the harmonic vibrational frequencies and rotational constants show good agreement. © 2000 Elsevier Science B.V. All rights reserved.

1. Introduction

Cytosine, as a nucleic acid base, has been the subject of several experimental [1–3] and theoretical [4–11] studies in the gas phase. The cytosine molecule may exist in various tautomeric forms [4] differing from each other by the position of the hydrogens, which may be bound to either ring nitrogen atoms or oxygen atoms (see Fig. 1). Matrix-isolation infrared studies of cytosine [2] identified the amino-oxo (C1) and the amino-hydroxy (C3) tautomeric forms at appreciable concentrations; the

imino-oxo (C2) form was predicted to be much less abundant in vacuum than in solution [12]; while in aqueous solution and crystal phase cytosine adopts predominantly the C1 form [2]. This change of the tautomeric equilibrium between different phases indicates the importance of environment in the determination of the order of stability of nucleic acid bases tautomers.

In spite of this fact, studies on solvent effects have not been completely characterized at a high calculation level. Previous works of Paglieri et al. [13] include solvent effects by means of the Onsager reaction field theory [14] in the framework of the density functional theory (DFT). Also, Colominas et al. [15] examine the influence of solvent using self-consistent reaction field and Monte Carlo free energy

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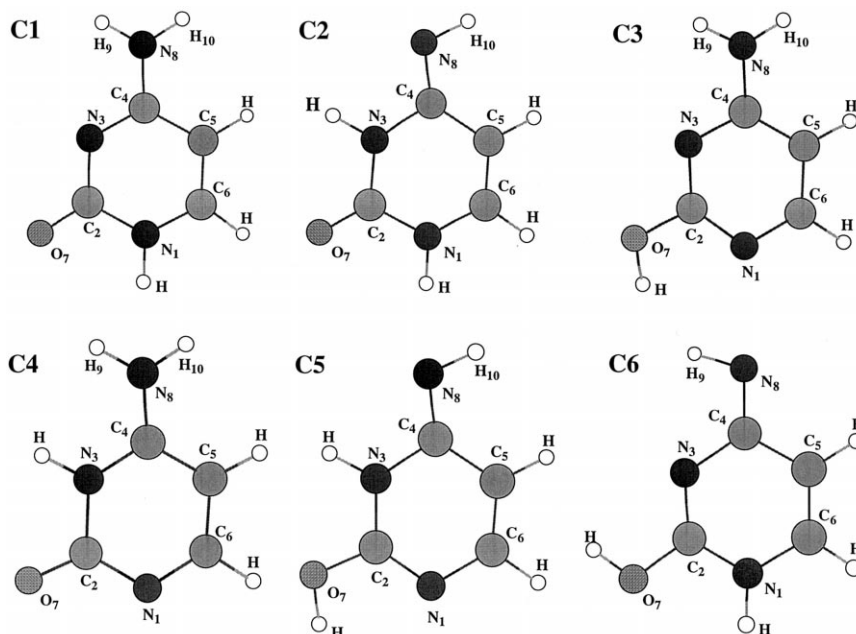


Fig. 1. Cytosine tautomers.

perturbation simulations at AM1 and HF/6-31G* levels.

In this Letter we have carried out a theoretical analysis of the different tautomers of the cytosine molecule by using B3LYP and MP2 methods with the 6-31++G** basis set. Solvent effects have been considered by means of two different continuum models. Geometrical optimization allows the analysis of the relative stability, rotational constants, vibrational frequencies with their corresponding intensities, and the dipole moments of the different tautomers. The theoretical results are confronted with experimental data.

2. Computational details

Calculations were carried out with the GAUSSIAN 94 [16] package program. MP2 perturbation theory [17] and DFT methodology with the B3LYP hybrid functional [18,19] and 6-31++G** basis set have been selected. The inclusion of polarized and diffuse functions and correlated methods are mandatory in

the description of cytosine molecule due to the non-planarity of the amino group [9].

To study the solvent effect we have employed the self-consistent reaction field method. In this methodology the solute molecule is enveloped in a cavity surrounded by a continuum with a dielectric constant. In this work we use a value of 78.4 to simulate aqueous medium. Applications of this method have been proved to yield reliable results [20–22]. Two approaches for environment simulation have been used. Rivail et al.'s method [23–26] where multipolar expansions in an ellipsoidal cavity are employed (**I**). And the self-consistent isodensity polarized continuum model developed by Tomasi et al. [27,28], where the cavity is defined as an isodensity surface of the molecule and the isosurface and the electron density are coupled (**II**).

Full geometry optimizations in the gas phase and in aqueous media have been carried out for the different tautomers with **I** and **II** methods. It is important to note that **II** method requires a very large computational cost with respect to **I**. For this reason, the **I** model, for calculations including solvent effects, has been selected. Frequency calculations have been restricted at the B3LYP (**I**) level.

3. Results and discussion

3.1. Relative stabilities and geometries

Relative energies of the six tautomers in the gas phase and in aqueous media are listed in Table 1. In the gas phase, the stability order is as follows: $C1 > C3 > C2 > C4 > C5 > C6$ and $C3 > C1 > C2 > C4 > C5 > C6$ at B3LYP and MP2 computing levels, respectively. Clearly, both methods show that C1, C2 and C3 tautomers are more stable than C4, C5 and C6. B3LYP present the former tautomers very close in energy, in a narrow range of 1.85 kcal/mol while MP2 calculations increases this range up to 3.31 kcal/mol, being now C3 the most stable tautomer. These results can be related with previous theoretical studies presented by Paglieri et al. [13], Kobayashi [10] and Leszczynski [11] and experimental studies where, according to infrared data [2], C1 and C3 tautomers exist in both argon and nitrogen matrices, being the C3 conformer present in higher concentrations. However, C1 is the only tautomeric form present in the solid state [29]. Kobayashi [10] carried out a CCSD(T) energetic study of the C1, C2 and C3 tautomeric forms of the cytosine in gas phase; they conclude that the relative energy of this conformers was $C3 < C2$ according with experimental studies [2]. This is different of the results obtained with the DFT methodology, that is, $C1 < C2$ [10,13]. This conclusion coincides with our gas phase results at MP2 level. However, when energetic differences become very small, as it is in this case (differences smaller than 1 kcal/mol between C1 and C3 conformers), thermal and zero-point energies can be important. In order to test this possibility, Gibbs free energies of these tautomers are calculated at 15 and

Table 1
Relative energy (kcal/mol) of the six tautomers of cytosine

	Gas phase		Aqueous media		
	B3LYP	MP2	B3LYP (I)	B3LYP (II)	MP2 (I)
C1	0.00	1.53	0.00	0.00	0.00
C2	1.85	3.31	5.70	5.89	5.84
C3	0.40	0.00	8.35	6.44	5.52
C4	6.99	8.89	5.64	4.37	6.28
C5	13.60	14.48	20.82	20.42	20.12
C6	18.74	18.94	22.73	22.47	21.88

Table 2

Dipole moment (debye) for the six tautomers of cytosine

	Gas phase		Aqueous media		
	B3LYP	MP2	B3LYP (I)	B3LYP (II)	MP2 (I)
C1	6.86	7.54	10.11	9.29	10.64
C2	5.03	5.69	7.10	6.48	7.77
C3	3.47	3.61	4.49	4.67	4.62
C4	8.35	8.68	12.13	11.96	12.15
C5	1.90	2.27	3.63	2.59	4.11
C6	5.15	5.55	8.34	7.47	8.82

298.15 K at B3LYP level and the difference of this thermodynamic variable between C1 and C3 is 0.62 and 0.95 kcal/mol, respectively. Therefore, inclusion of thermal and zero-point energies yields small changes.

Inclusion of environment by using B3LYP at **I** and **II** continuum models changes the stability order: $C1 > C4 > C2 > C3 > C5 > C6$; while MP2 at **I** model shows the following order: $C1 > C3 > C2 > C4 > C5 > C6$. In water solution C1 is the predominant species as the experimental studies stated [1]. Solvent inclusion destabilizes conformers C2, C3, C5 and C6 with respect to C4 and C1. C2, C3 and C4 tautomers are close in energy, in a range of 0.32–2.71 kcal/mol. These results can be explained by the large values of the dipole moments of C4 and C1 with respect to the rest of tautomers. In Table 2, the dipole moments calculated in the gas phase and aqueous media are listed.

Tautomerization energy calculated as a difference in energy between two tautomers in the gas phase and in aqueous media are reported in Table 3. The inclusion of solvent effect increases the tautomerization energy of the following processes: $C1 \rightleftharpoons C2$, $C1 \rightleftharpoons C3$ due to the large stabilization of the C1 tautomer with respect C2 and C3 when solvent effects are considered. A similar trend is found for $C2 \rightleftharpoons C5$ while that the large stabilization of the C4 with respect C3 makes that the tautomerization energy for $C3 \rightleftharpoons C4$ equilibrium undergoes an appreciable diminution.

In order to taste the possible importance of some specific solvent effects like H-bonds, calculations with the inclusion of one water molecule (see Fig. 2) to the C1 and C2 conformers have been carried out. The energetic results obtained, for the tautomeric

Table 3

Tautomerization energies (kcal/mol)

	Gas phase		Aqueous media		
	B3LYP	MP2	B3LYP (I)	B3LYP (II)	MP2 (I)
C1 \rightleftharpoons C2	1.85	1.79	5.70	5.89	5.84
C1 \rightleftharpoons C3	0.40	1.53	8.35	6.44	5.52
C2 \rightleftharpoons C5	11.75	11.16	15.11	14.53	14.28
C3 \rightleftharpoons C4	6.59	8.89	2.70	2.07	0.76
C3 \rightleftharpoons C5	13.19	14.48	12.47	13.98	14.60
C1 + H ₂ O \rightleftharpoons C2 + H ₂ O	–	–	6.59	–	–

equilibrium, are shown in Table 3. The value was of 6.59 kcal/mol. If it is compared with the value obtained only including electrostatic interactions (5.70 kcal/mol), it can be stated that these last effects are much more important than specific solvent effects. Therefore, continuum models can be presented as good models for representing reality, even more when the solvent has a high dielectric constant.

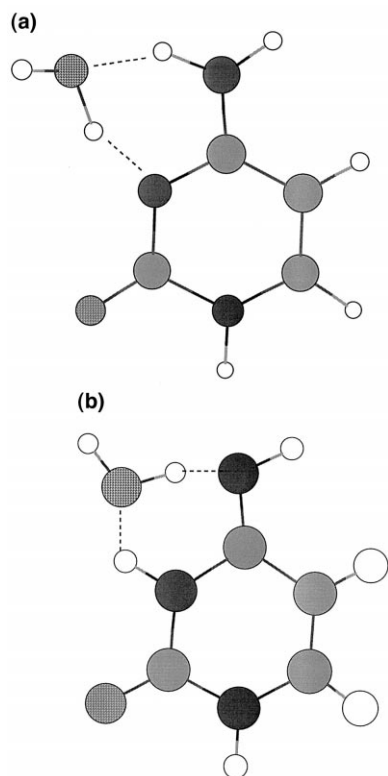


Fig. 2. (a) C1 tautomer with a discrete water molecule. (b) C2 tautomer with a discrete water molecule.

In Table 4 relevant geometrical parameters of tautomer C1 are reported. The geometrical parameters of the tautomers C2, C3, C4, C5 and C6 are available upon request. An analysis of the results shows that aqueous media have an influence on the molecular geometries. In particular, the dihedral angles values undergo an appreciable change. However, there is a significant difference between **I** and **II** models with B3LYP method of calculation. In the former the value of the dihedral angle $\tau(\text{N}_3\text{C}_4\text{N}_8\text{H}_9)$, associated with the non-planarity of the amino group, increases, as also happens at MP2 (**I**) level. With the **II** model another effect is found. In this case the amino group almost becomes planar on going from the gas phase to aqueous medium.

In order to check this result we have carried out calculations including a discrete water molecule that interacts with the amino group forming two hydrogen bonds, $\text{N8-H9}\dots\text{O}$ and $\text{O-H}\dots\text{N3}$, along a six-member ring (see Fig. 2). For B3LYP (**I**) method, the value of the $\tau(\text{N}_3\text{C}_4\text{N}_8\text{H}_9)$ dihedral angle is maintained to 8.88 while a small increase of 3.00 is obtained at B3LYP (**II**). Therefore, this different behavior can be attributed to the solvent simulation, **I** and **II**, instead of specific interactions of the solvent.

3.2. Vibrational analysis

A normal mode analysis has been carried out. Vibrational frequencies, IR intensities and rotational constants calculated with B3LYP/6-31++G** level at 15 K for the C1 tautomer, in the gas phase and taken into account the solvent effects by means of **I** model, are listed in Table 5. Available experimental data are reported for the sake of clearness.

Table 4

Selected geometric parameters (distances in Å and angles in degrees) for the C1 tautomer

Parameter	Gas phase		Aqueous media			
	B3LYP	MP2	B3LYP (I)	B3LYP (II)	MP2 (I)	exp. ^a
$r(\text{N}_1\text{C}_2)$	1.427	1.417	1.423	1.409	1.392	1.397
$r(\text{C}_2\text{N}_3)$	1.371	1.381	1.358	1.363	1.365	1.355
$r(\text{N}_3\text{C}_4)$	1.321	1.321	1.335	1.335	1.339	1.337
$r(\text{C}_4\text{C}_5)$	1.442	1.437	1.437	1.433	1.429	1.424
$r(\text{C}_5\text{C}_6)$	1.361	1.361	1.361	1.360	1.363	1.339
$r(\text{C}_6\text{N}_1)$	1.356	1.359	1.359	1.360	1.360	1.365
$r(\text{C}_2\text{O}_7)$	1.224	1.231	1.248	1.240	1.256	1.238
$r(\text{C}_4\text{N}_8)$	1.361	1.371	1.354	1.350	1.367	1.333
$\angle(\text{N}_1\text{C}_2\text{N}_3)$	116.35	116.26	117.65	117.58	117.58	120.32
$\angle(\text{C}_2\text{N}_3\text{C}_4)$	120.36	119.85	120.21	120.03	119.76	120.02
$\angle(\text{N}_3\text{C}_4\text{C}_5)$	123.92	124.38	122.74	123.12	123.13	121.68
$\angle(\text{C}_4\text{C}_5\text{C}_6)$	116.12	116.11	116.78	116.49	116.84	117.53
$\angle(\text{C}_5\text{C}_6\text{N}_1)$	119.97	119.67	119.63	120.05	119.20	121.12
$\angle(\text{C}_6\text{N}_1\text{C}_2)$	123.28	123.73	122.99	122.74	123.45	120.32
$\angle(\text{N}_1\text{C}_2\text{O}_7)$	118.17	118.86	118.45	118.35	119.06	118.93
$\angle(\text{N}_3\text{C}_4\text{N}_8)$	116.95	116.87	117.67	117.32	117.43	118.21
$\tau(\text{N}_3\text{C}_4\text{N}_8\text{H}_9)$	6.43	14.41	8.20	0.00	18.31	–
$\tau(\text{N}_3\text{C}_4\text{N}_8\text{H}_{10})$	170.58	157.96	170.76	179.95	158.97	–
$\tau(\text{C}_5\text{C}_4\text{N}_8\text{H}_9)$	185.53	191.51	187.27	180.00	195.27	–
$\tau(\text{C}_5\text{C}_4\text{N}_8\text{H}_{10})$	349.68	335.06	349.84	359.95	336.17	–

^aRef. [30].

Harmonic vibrational frequencies are not scaled as was suggested by Pople et al. [31].

A comparison between the values in the gas phase and in aqueous media shows some differences; for instance, the value of vibrational frequency for ν_6 and ν_{28} , associated with the bending and stretching of $\text{C}_2=\text{O}_7$ bond decreases significantly 46 and 111 cm^{-1} , respectively. In general, most absorption peaks are more intense in aqueous media than in the gas phase. In particular, a strong shift for the scissors vibration of the amino group (ν_{26}) from 146 to 1734 km/mol can be observed and also in the mode associated with the bending of C_4-N_8 bond (ν_2), that changes from 192 to 411 km/mol . However, the intensity of the band corresponding to the stretching of $\text{C}_2=\text{O}_7$ bond (ν_{28}) is found to decrease significantly, from 775 to 468 km/mol .

When theoretical and experimental data are compared some differences are detected. In the region of 100–1000 cm^{-1} , the theoretical vibrational frequency values are lower than the experimental ones, except ν_5 and ν_{12} . An opposite trend is found in the

upper region, except for ν_{28} . Experimental IR intensities are smaller than the corresponding theoretical values, except for ν_4 , ν_8 , ν_9 , ν_4 , ν_{17} , ν_{19} and ν_{32} .

Our solvent theoretical calculations give frequency modes with lower values than the obtained by Paglieri et al. [13], in the 100–550 cm^{-1} region. An opposite trend is found in the upper region. The main difference is that, as also occurs for the B3LYP (II) calculations, the solvent model employed by Paglieri et al. [13], based in a spherical cavity, renders the amino group ring-coplanar when solvent effects are included.

In Table 5 rotational constants are displayed. Their analysis shows a good agreement between the theoretical and experimental values. Small changes are found on going from gas phase to aqueous medium.

4. Conclusions

We have presented B3LYP and MP2 calculations, with 6-31++G** basis set, of the six tautomers

Table 5

Vibrational frequencies (cm^{-1}), IR intensities (in parentheses, km/mol) and rotational constants A , B and C (MHz) calculated at 15 K for C1

Results obtained with B3LYP/6-31 + + G * * computing method and **I** model of aqueous media

	Mode ^a	Gas phase	Aqueous media I	Exp. ^b
ν_1	ring def oopl	134 (2)	110 (41)	197
ν_2	C_4N_8 b oopl	176 (192)	161 (411)	232
ν_3	C_2O_7 C_4N_8 b oopl	202 (42)	192 (49)	360 (8)
ν_4	N_8H_2 C_2O_7 b	358 (3)	360 (5)	409 (20)
ν_5	ring def oopl	397 (21)	398 (25)	330 (30)
ν_6	C_2O_7 C_4N_8 b	526 (11)	480 (14)	532 (5)
ν_7	N_8H_2 tors, C_2O_7 b	532 (4)	534 (7)	537 (6)
ν_8	ring s	545 (3)	549 (2)	575 (6)
ν_9	N_8H_9 tors	577 (2)	585 (12)	614 (40)
ν_{10}	N_1H b oopl	626 (66)	603 (112)	637 (8)
ν_{11}	C_5H N_1H b oopl, ring def oopl	724 (30)	720 (28)	747 (5)
ν_{12}	C_4N_8 C_5H b oopl	771 (37)	774 (18)	623 (6)
ν_{13}	C_2O N_1H b oopl	764 (6)	781 (14)	818 (14)
ν_{14}	ring breathing	768 (15)	784 (56)	781 (41)
ν_{15}	C_5H C_6H ooph oopl	961 (1)	944 (8)	—
ν_{16}	N_1C_2 C_4C_5 s, ring def	925 (4)	967 (1)	—
ν_{17}	ring def in pl	988 (0)	991 (10)	1090 (53)
ν_{18}	ring wag in pl, C_2O_7 b	1088 (42)	1100 (57)	1087 (8)
ν_{19}	C_5C_6 C_6N_1 s	1128 (3)	1132 (2)	1124 (36)
ν_{20}	C_5H C_6H b ooph, N_1H b	1220 (52)	1226 (136)	1192 (70)
ν_{21}	N_3C_2 C_4N_8 s	1264 (30)	1294 (36)	1244 (36)
ν_{22}	C_5H C_6H b in ph, N_1H b	1359 (52)	1364 (222)	1337 (46)
ν_{23}	N_3C_4 C_4C_5 s, N_1H b	1443 (81)	1435 (204)	1422 (56)
ν_{24}	ring s N_8H_9 N_8H_{10} C_5H C_5H b	1508 (145)	1493 (846)	1475 (189)
ν_{25}	N_3C_4 C_4C_5 s, N_1H b	1570 (167)	1556 (185)	1539 (97)
ν_{26}	N_8H_2 sciss, C_4N_8 s	1638 (146)	1611 (1734)	1595 (71)
ν_{27}	C_5C_6 N_3C_4 s	1692 (503)	1656 (602)	1656 (424)
ν_{28}	C_2O_7 s	1774 (775)	1673 (468)	1720 (872)
ν_{29}	C_6H s	3211 (3)	3228 (1)	—
ν_{30}	C_5H s	3236 (3)	3253 (1)	—
ν_{31}	N_8H_9 N_8H_{10} s in ph	3609 (92)	3588 (200)	3441 (209)
ν_{32}	N_1H s	3629 (72)	3626 (141)	3471 (143)
ν_{33}	N_8H_9 N_8H_{10} s oopl	3750 (51)	3715 (101)	3565 (81)
A		3852.18	3868.66	3871.55 ^c
B		2011.55	2007.36	2024.93 ^c
C		1321.66	1321.82	1330.31 ^c

^aAbbreviations: b = bending; s = stretching; oopl = out-of-ring plane; ooph = out of phase; in ph = in phase; in pl = in-ring plane; def = deformation.

^b ν_1 and ν_2 are obtained from crystalline solid, ν_3 , ν_4 and ν_6 are obtained in N_2 matrix. The rest of frequencies from argon matrix at 15 K [2].

^cRef. [3].

of cytosine. Simulation was performed for both gas phase and aqueous solution on the basis of the self-consistent reaction field theory by means of the Rivail's (**I**) and Tomasi's (**II**) models. The significant influence of solvent on the order of stability of the tautomers has been clearly shown in the present

study. Some conclusions from the present work may be delineated as follows:

(1) In the gas phase, at the MP2 level of calculation, the order of stability obtained was: $\text{C3} > \text{C1} > \text{C2} > \text{C4} > \text{C5} > \text{C6}$ with an energy difference between C3 and C1 of 1.53 kcal/mol. The order of

stability obtained at the B3LYP level of calculation was: C1 > C3 > C2 > C4 > C5 > C6, being the energy difference between C1 and C3 of 0.40 kcal/mol.

(2) The order of magnitude of purely electrostatic solvent effects is much greater than the corresponding to the specific interactions as the H-bond.

(3) The electrostatic solvent effect inclusion yields an appreciable change in the stability order of cytosine tautomers. The continuum environment due to the larger values of the corresponding dipole moment favors C1 and C4 forms. In aqueous media, B3LYP (I and II) and MP2 (I) levels render the C1 tautomer as the most abundant form.

(4) The amino group becomes ring-coplanar on going from the gas phase to aqueous medium at the B3LYP (II) method. However, the dihedral angle related with this motion increases from 6.43 to 8.20° and from 14.41 to 18.31° with B3LYP (I) and MP2 (I) calculation levels, respectively.

(5) A comparison of IR spectrum of the C1 tautomer obtained in the gas phase, aqueous media and experimental data shows that the inclusion of solvent decreases significantly the bending and stretching modes of the C₂=O₇ bond; absorption peaks are more intense in aqueous media than in the gas phase.

(6) Present theoretical results emphasize the role of solvent effects and the influence of the environment simulations by means of continuum models.

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