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Quantum Chemical Studies on Conformations of Indoles

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ABSTRACT

All the possible tautomeric equilibria and conformers of 1-, 2- & 1, 2- substituted indoles in aqueous solution were studied by semi-empirical methods. All possible tautomeric equilibria and conformers of the indoles were considered to determine the most stable forms. The AM1/COSMO & PM3/COSMO calculations indicate that the compound 2-hydroxymethylindole prefers anti-anti & anti-anti forms, 2-formylindole anti-, ethyl indole-2-carboxylate syn-syn, indole-2-carboxylic acid syn-syn, indole-2-carbohydrazide syn-syn, 2-formyl-1-methylindole syn forms respectively over other tautomeric forms by different percentages.

Keywords: Indoles, Conformers, Semi-empirical methods, AM1/COSMO & PM3/COSMO methods.

INTRODUCTION

Indoles are associated with the different biological properties. They exhibit antibacterial, antioxidant, cytotoxic, insecticidal and pronounced hallucinogenic activities. Some of the derivatives of indole are applied as antibiotics in pharmaceuticals. Because of the broad use of indoles in a wide range of fields, such as biochemistry, biology, pharmacology, and agricultural sciences to name a few, indole syntheses that are mild and convenient are of great importance in organic chemistry. The amino acid, tryptophan, and its derivatives such as l-5-Hydroxytryptophan and N-acetyl-DL-tryptophan are important indole derivatives [1]. Serotonin and melatonin are also important biochemically active molecules [2]. There are hundreds of alkaloid derivatives of indole, many of which are found in nature. Some indole alkaloids have been used medicinally such as harmine [3]. Indole derivatives are important pharmaceuticals or pharmaceutical intermediates [4] and hence their theoretical studies have been done continuously [5].

As well known, the reactivity of a compound depends on its tautomeric and conformational structures. Therefore, it is of importance to investigate the tautomeric and conformational equilibrium for compounds. In this study, the tautomeric equilibrium constant values of indole (**1**), 2-methylindole (**2**), 2-hydroxymethylindole (**3**), 2-formylindole (**4**), ethyl indole-2-carboxylate (**5**), indole-2-carboxylic acid (**6**), indole-2-carbohydrazide (**7**), 1-

methylindole (**8**), 1,2-dimethyl indole (**9**), 2-formyl-1-methylindole (**10**), and ethyl -1-methylindole-2-carboxylate (**11**), which can exist as different major tautomers according to the solvent and the mode of the substitutions have been computationally calculated in aqueous solution by means of AM1 [6] and PM3 [7] semi-empirical methods.

Computational Methods

Theoretical calculations were carried out at the restricted Hartree-Fock Level (RHF) using AM1 and PM3 semi-empirical SCF-MO methods in the MOPAC-98 program[8] , implemented on an Intel Celeron 400 MHz computer using a relative permittivity of 78.4 corresponding to water, with up to 60 surface segments per atom for the COSMO model being used to construct a solvent accessible surface area based on van der Waals radii. All the structures were optimized to gradient norm of 0.1±1.0 in the aqueous phase, using the eigenvector (EF). The absolute entropies of all structures were calculated from a complete vibrational analysis. Enthalpies were corrected to free energies using calculated entropies. Initial estimates of the geometry of all the structures were obtained by a molecular mechanic program (CS Chem. Office Pro for Windows)[9] followed by full optimization of all geometrical variables (bond angles, bond lengths, and dihedral angles), without any symmetry constraint, using the semi-empirical AM1 and PM3 quantum chemical methods in the MOPAC-98 program.

RESULTS & DISCUSSION

In this study, we considered only *anti* (i.e. dihedral angle 1234 = 180^{O}) and *syn* (i.e. dihedral angle 1234 = 0^{O}) conformers (**Scheme 1**). The AM1 and PM3 calculated values for tautomeric pairs (**Scheme-1, &-2**) have been used to be able to calculate free energy of the individual conformers. The AM1 and PM3 calculated mole fractions for individual conformers in aqueous solution are given in **Tables 1** and **2**. The mole fraction of individual tautomers can be calculated using the following equations:

$$\text{anti} \overset{K_c}{\leftrightarrow} \text{syn}$$

According to equilibrium given above,

$$\boldsymbol{K_c = N_s / N_t \text{ and } N_s + N_t = 1}$$

can be written, where K_C is conformational equilibrium constant, N_S and N_t are the mole fractions of *syn* and *anti* conformers.

$$\mathbf{N_s = 1 / 1 + K_c \text{ and } Nt = Kc / 1 + K_c}$$

The overall free energy of the compound was calculated by the following equations.

$$\Delta G_f = [\mathbf{N_s}]\ [\Delta G_s] + [\mathbf{N_t}]\ [\Delta G_t]$$

Where ΔG_f is overall free energy of compound, ΔG_s and ΔG_t are free energies of confirmers' *s* and *t*.
In this study, the equilibrium between *anti* and *syn* conformers were not investigated experimentally [10-12] but possible anti and syn conformers were calculated by AM1 and PM3 methods.

Theoretically, there are few possible tautomeric species for investigated indole derivatives. These are given in scheme1 and 2. According to the calculated free energies for tautomers, **1a** form is more stable than **1b** by 2.06 and 3.36 kcal/mol and **1a** form is more stable than **1c** form by 23.46 and 21.02 kcal/mol, byAM1&PM3 respectively. The calculated mole fractions of the

tautomers support these results. The compound **2** exhibits four tautomeric forms (2a, 2b 2c &2d). The calculated AM1 & PM3 free energies for tautomeric forms show that 2a form is more stable than the others. The compound **3** exhibits eight tautomeric forms shown in **scheme-1** as

3a1 ↔ 3a2, 3b1 ↔ 3b2, 3c1 ↔ 3c2, 3d1 ↔ 3d2

The calculated free energies for tautomers show that 3a1 form is more stable than 3a2 by -2.42 and -3.36 kcal/mol, 3b1 is more stable than 3b2 by 0.83 and -1.89 kcal/mol, 3c1 is more stable than 3c2 by 005 and -4.5 kcal/mol and 3d1 is more stable than 3d2 by 2.86 and -4.37, by AM1 &PM3 respectively. According to the calculated AM1 and PM3 mole fractions of tautomer pairs, 3a prefers 3a1 form with a preference of 98 and 100% to 3a2; 3b prefers 3b1 form with a preference of 80 and 96% to 3b2, by AM1 and PM3, respectively. 3c prefers both 3c1 form with preference of 51% and 3c2 form with a preference of 49% in AM1 calculation and prefers only 3c1 form with a preference of 100% in PM3 calculation. 3d prefers 3d1 form with a preference of 99 and 100% to 3d2, by AM1 and PM3, respectively.

The compound **4** exhibits four tautomeric forms, shown in **scheme 1** as

4a1 ↔ 4a2, 4b1 ↔ 4b2

The calculated free energies for tautomers show that 4a1 form is more stable than 4a2 by 44.3, 29.03 kcal/mol and 4b1 form is more stable than 4b2 by 25.57, 29.22 kcal/ mol, by AM1 and PM3, respectively. According to the calculated AM1 and PM3 mole fractions of tautomer pairs, 3a prefers 3a1 form with a preference of 100 and 100% to 3a2, by AM1 and PM3, respectively.

The compound **5** exhibits eight tautomeric forms shown in **scheme 2** as

5a1 ↔ 5a2, 5b1 ↔ 5b2, 4c1 ↔ 5c2, 5d1 ↔ 5d2

The calculated free energies for tautomers show that 5a1 form is more stable than 5a2 by 24.64 and 26.07 kcal/mol5b1 form is more stable than 5b2 by 90.71 and 6.9 kcal/mol, by AM1 and PM3, respectively. 5c1 form is more stable than 5c2 by 24.67 and 27.75 kcal/mol, and 5d1 form is more stable than 5d2 by 25.90 and 27.98 kcal/mol, by AM1 and PM3, respectively. According to the calculated AM1 and PM3 mole fractions of tautomer pairs, 5a prefers 5a1 form with a preference of 100 and 100% to 5a2, 5b prefers 5b1 form with a preference of 100 and 100% to 5b2, 5c prefers 5c1 form with a preference of 100 and 100% to 5c2, and 5d prefers 5d1 form with a preference of 100 and 100% to 5d2, by AM1 and PM3, respectively.

The compound **6** exhibits eight tautomeric forms, shown in **scheme 2 as**

6a1 ↔ 6a2, 6b1 ↔ 6b2, 6c1 ↔ 6c2, 6d1 ↔ 6d2

The calculated free energies for tautomers show that 6a1 form is more stable than 6a2 by 5.5 and 7.5 kcal/mol, the 6b1 form is more stable than 6b2 by 3.78 and 8.28 kcal/mol, 6c1 form is more stable than 6c2 by 7.07 and 9.25 kcal/mol and 6d1 form is more stable than 6d2 by 5.54 and 8.19 kcal/mol, by AM1 and PM3, respectively. According to the calculated AM1 and PM3, the mole fractions of tautomer pairs, 6a prefers 6a1 form with a preference of 100 and 100% to 6a2,. 6b prefers 6b1 form with a preference of 100 and 100% to 6b2, 6c prefers 6c1 form with a preference of 100 and 100% to 6c2 and 6d prefers 6d1 form with a preference of 100 and 100% to 6d2, by AM1 and PM3, respectively.

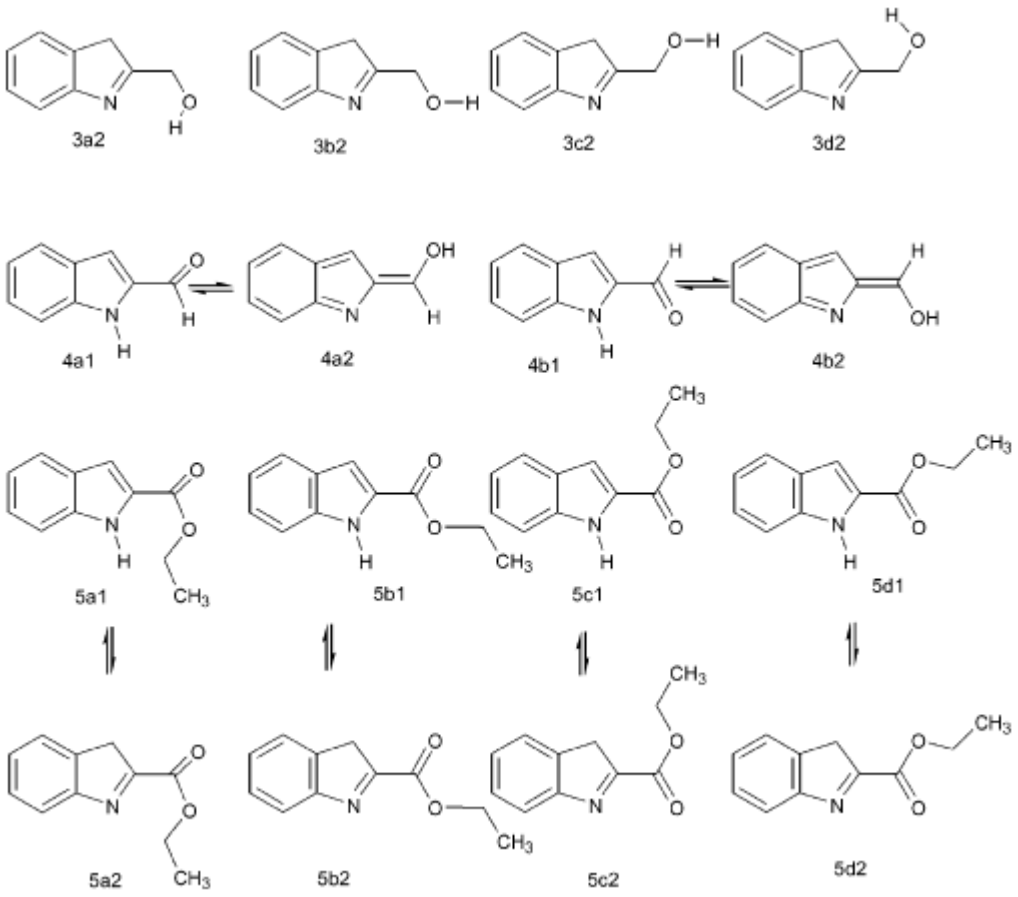
The compound **7** exhibits eight tautomeric forms, shown in **scheme 2** as

7a1 ↔ 7a2, 7b1 ↔ 7b2, 7c1 ↔ 7c2, 7d1 ↔ 7d2

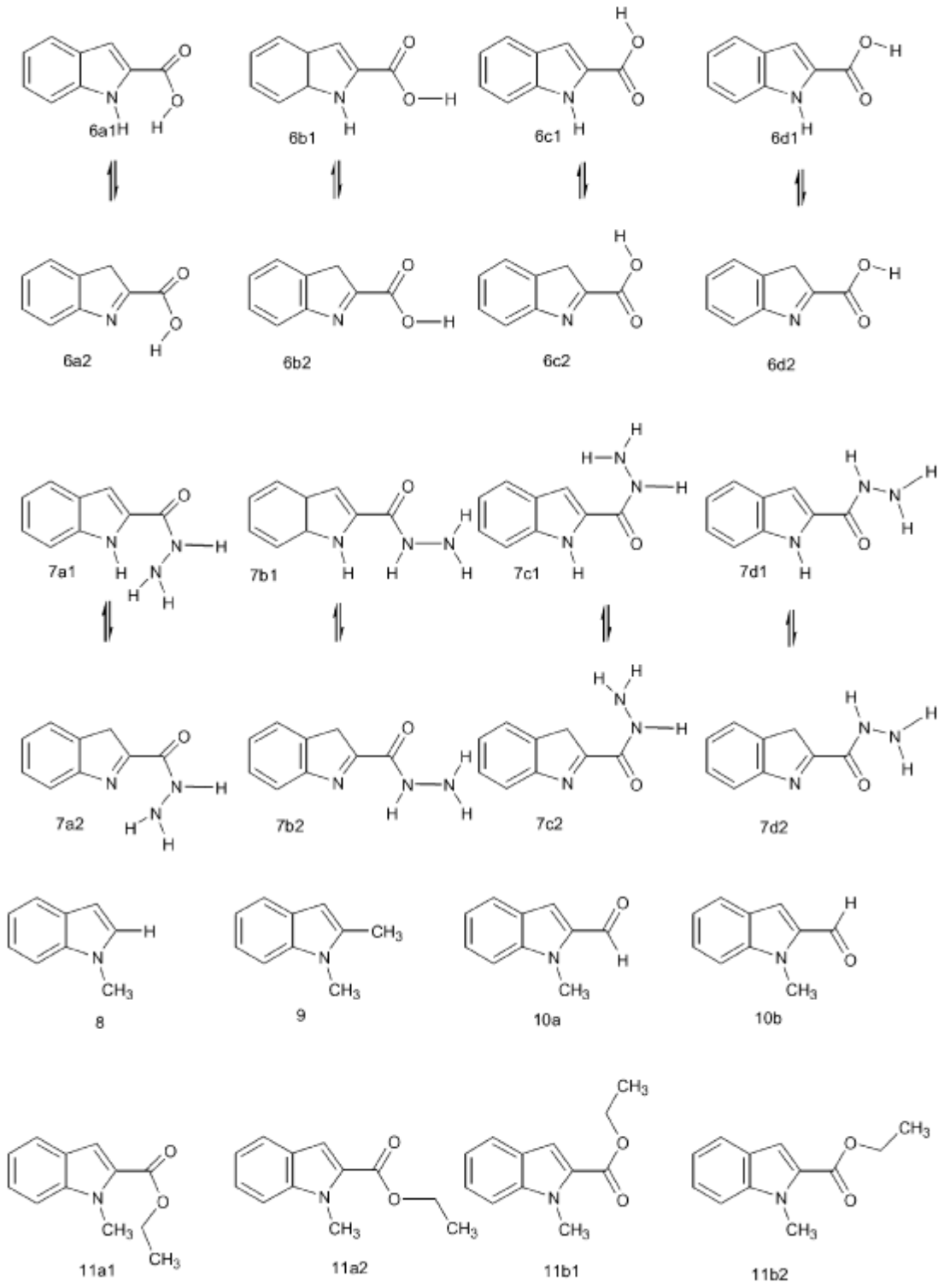
The calculated free energies for tautomers show that 7a1 form is more stable than 7a2 by 3.77 and 4.14 kcal/mol, 7b1 form is more stable than 7b2 by 2.53 and 5.43 kcal/mol, 7c1 form is more stable than 7c2 by 3.09 and 7.61 kcal/mol, and 7d1 form is more stable than 7d2 by 5.81 and 8.38 kcal/mol, by AM1 and PM3, respectively. According to the calculated AM1 and PM3 the mole fractions of tautomer pairs, 7a prefer 7a1 form with a preference of 100 and 100% to 7a2, 7b prefers 7b1 form with a preference of 99 and 100% to 7b2, 7c prefers 7c1 form with a preference of 99 and 100% to 7c2, and 7d prefers 7d1 form with a preference of 100 and 100% to 7d2, by AM1 and PM3, respectively. Since compounds 8, 9, 10 and 11, do not exhibit any tautomeric forms, tautomeric equilibrium for these compounds has not been studied. The impossibility of existence of the other tautomeric forms, can easily be deduced from the high heats of formation and free energy values (**Table-1 and -2**).

For compounds 3, 5, 6, 7 and 11 *anti- anti* (i.e. a dihedrals 1234 and 2356 180^{O}), *syn -syn* (i.e. b dihedrals 1234 and 2356 0^{O}), *anti-syn* (i.e. c dihedral 1234 180^{O} and dihedral 2356 0^{O}), *syn -anti* (i.e. d dihedral 1234 0^{O} and dihedral 2356 180^{O}) and in the compounds 4 and 10 *anti* (i.e. a dihedral 1234 180^{O}), *syn* (i.e. b dihedral 1234 0^{O}) conformers were considered.

As can be seen from the AM1 and PM3 calculated mole fraction values in the aqueous phase calculations (**Tables 1** and **2**) it is indicated that in AM1 calculations, compound **3** prefers *syn -anti* (3a) and *anti- anti* forms (3d) with preference of 72 and 24%, respectively. On the other hand, in PM3 calculations, it prefers *syn -anti* (3a), *anti-syn* (3c) *anti-anti* (3d) forms with preference of 34, 37 and 28%, respectively.



Scheme-1


6a1H
6b1
6c1
6d1
6a2
6b2
6c2
6d2
7a1
7b1
7c1
7d1
7a2
7b2
7c2
7d2
8
9
10a
10b
11a1
11a2
11b1
11b2

Scheme-2

Table-1 The AM1 calculated thermodynamic properties of indoles derivatives in aqueous solution (ε = 78.4)

Compound	ΔH_f (kcal/mol)	ΔS (kcal/mol/K)	ΔG_f^a (kcal/mol)	Mol fraction of tautomers [b]	$\Delta G_{(ave)}^c$ (kcal/mol)	Relative stability (kcal/mol)	Overall mol fractions of tautomes [d]	Overall ΔG_f^a (kcal/mol)
1a	45.40	79.13	21.82	0.97	21.88	0.00		21.88
1b	47.28	78.53	23.88	0.03		2.06		
1c	68.80	78.93	45.28	0.00		23.46		
2a	37.46	84.25	12.45	0.97	12.41	0.00		12.41
2b	39.44	83.56	14.54	0.03		2.19		
2c	65.61	85.83	40.04	0.00		27.69		
2d	41.51	84.84	16.23	0.00		3.88		
3a1	-12.80	88.58	-39.20	0.98	-39.15	0.00	0.72	-38.92
3a2	-10.04	87.36	-36.78	0.02				
3b1	-10.85	89.74	-37.60	0.80	-37.43	1.71	0.04	
3b2	-10.74	87.35	-36.77	0.20				
3c1	-9.35	88.77	-35.80	0.52	-35.78	3.37	0.00	
3c2	-9.63	87.65	-35.75	0.48				
3d1	-12.04	88.88	-38.53	0.99	-38.50	0.65	0.24	
3d2	-9.62	87.40	-35.67	0.01				
4a1	9.38	86.46	-35.14	1.00	-35.14	0.00	1.00	-35.14
4a2	34.65	85.54	9.16	0.00				
4b1	8.04	86.42	-17.70	1.00	-17.70	17.44	0.00	
4b2	33.39	85.63	7.87	0.00				
5a1	-44.61	97.01	-73.53	1.00	-73.52	3.17	0.25	-76.52
5a2	-40.17	96.34	-68.88	0.00				
5b1	-48.76	91.42	-76.01	1.00	-76.01	0.68	0.00	
5b2	-42.51	93.32	14.70	0.00				
5c1	-45.02	96.15	-73.67	1.00	-73.67	3.02	0.75	
5c2	-40.22	96.56	-69.00	0.00				
5d1	-48.31	95.23	-76.70	1.00	-76.70	0.00	0.02	-77.32
5d2	-42.27	85.83	-70.80	0.00				
6a1	-48.09	90.61	-75.10	1.00	-75.10	2.42	0.03	
6a2	-42.78	89.99	-69.60	0.00				
6b1	-49.20	88.27	-75.50	1.00	-75.50	2.02	0.05	
6b2	-45.06	89.46	-71.72	0.00				
6c1	-49.78	87.10	-75.74	1.00	-75.74	1.78	0.05	
6c2	-42.88	86.55	-68.67	0.00				
6d1	-51.46	87.44	-77.52	1.00	-77.52	0.00	0.90	-5.13
6d2	-45.27	89.63	-71.98	0.00				
7a1	26.26	95.44	-2.18	1.00	-2.18	3.05	0.01	
7a2	29.13	92.43	1.59	0.00				
7b1	25.40	96.72	-3.42	0.99	-3.39	1.84	0.04	
7b2	27.43	95.06	-0.89	0.01				
7c1	26.62	94.50	-1.53	0.99	-1.50	3.73	0.00	
7c2	29.13	92.52	1.56	0.01				
7d1	22.50	93.06	-1.23	1.00	-5.23	0.00	0.95	
7d2	28.24	92.81	0.58	0.00				
8	51.55	87.25	25.55				1.00	25.55
9	43,84	91.79	16.49				1.00	16.49
10a	16.33	90.33	-10.58				0.09	-11.80
10b	15.70	92.60	-11.92				0.91	
11a	-37.35	104.64	-68.53				0.02	
11b	-40.85	97.73	-68.87				0.24	-70.31
11c	-37.95	101.05	-68.06				0.01	
11d	-40.39	101.16	-70.54				0.73	

[a] $\Delta G_f = \Delta H_f - T\Delta S$

[b] If a ↔ b, $N_a = 1 / [1 + K_t]$, $N_b = K_t / [1 + K_t]$; If a ↔ b ↔ c, $N_a = 1 / [1 + K_{t1} + K_{t3}]$, $N_b = K_t / [1 + K_{t1} + K_{t3}]$, $N_c = K_{t3} / [1 + K_{t1} + K_{t3}]$; If a ↔ b ↔ c ↔ d, $N_a = 1 / A$, $N_b = K_{t1} / A$, $N_c = K_{t1} K_{t2} / A$, $N_d = K_{t1} K_{t2} K_{t3} / A$; $A = 1 + K_{t1} + K_{t1} K_{t2} + K_{t1} K_{t2} K_{t3}$.

[c] Weighted average of tautomers $\Delta G_{f(ave)} = [N_{1a}] [\Delta G_{f1a}] + [N_{1b}] [\Delta G_{f1b}] + \ldots$

[d] anti ↔ syn $N_{t(anti)} = 1 / [1 + K_T]$, $N_{s(syn)} = K_T / [1 + K_T]$ $K_T = e^{(- \delta\Delta G / RT)}$ $R = 1.987 \times 10^{-3}$ kcal/mol and T = 298K.

[e] Overall $\Delta G_f = [Na][\Delta G_{f(a)}] + [N_b][\Delta G_{f(b)}] + [N_c][\Delta G_{f(c)}] + \ldots$

Table-2 The PM3 calculated thermodynamic properties of indoles derivatives in aqueous solution (ε = 78.4)

Compound	ΔH_f (kcal/mol)	ΔS (kcal/mol/K)	ΔG_f^a (kcal/mol)	Mol fraction of tautomers [b]	$\Delta G_{(ave)}^c$ (kcal/mol)	Relative stability (kcal/mol)	Overall mol fractions of tautomes [d]	Overall ΔG_f^a (kcal/mol)
1a	34.89	79.75	11.13	1.00	11.13	0.00		11.13
1b	38.14	79.35	14.49	0.00		3.36		
1c	55.98	79.95	32.15	0.00		21.02		
2a	25.15	86.67	-0.67	0.99	-0.64	0.00		-0.64
2b	28.35	87.63	2.24	0.01		2.91		
2c	51.90	87.13	25.93	0.00		26.60		
2d	33.07	82.34	8.52	0.00		9.19		
3a1	-18.34	89.60	-44.94	1.00	-44.94	0.05	0.34	
3a2	-14.35	89.32	-40.97	0.00				
3b1	-17.06	86.22	-42.76	0.96	-42.86	2.13	0.01	
3b2	-14.39	88.86	-40.87	0.04				-44.91
3c1	-18.43	89.12	-44.99	1.00	-44.99	0.00	0.37	
3c2	-14.09	88.59	-40.49	0.00				
3d1	-18.22	89.30	-44.83	1.00	-44.84	0.15	0.28	
3d2	-14.09	88.50	-40.46	0.00				
4a1	-7.06	86.37	-32.80	1.00	-32.80	044	0.32	
4a2	21.95	86.06	-3.77	0.00				-33.10
4b1	-7.51	86.35	-33.24	1.00	-33.24	0.00	0.68	
4b2	21.59	85.95	-4.02	000				
5a1	-58.79	100.40	-88.71	1.00	-88.71	0.00	079	
5a2	-53.87	96.52	-82.64	0.00				
5b1	-59.42	92.18	-86.90	1.00	-82.64	6.07	0.00	
5b2	-51.81	94.61	-80.00	0.00				-88.53
5c1	-61.40	96.97	-90.29	1.00	-80.00	8.71	0.00	
5c2	-53.79	96.48	-8254	0.00				
5d1	-59.53	95.25	-87.92	1.00	-87.92	0.79	0.21	
5d2	-51.66	94.89	-79.94	0.00				
6a1	-64.89	88.00	-91.11	1.00	-91.11	2.24	0.03	
6a2	-57.60	87.28	-83.61	0.00				
6b1	-65.43	87.78	-91.59	1.00	-91.59	1.76	0.04	
6b2	-57.23	87.53	-83.31	0.00				-93.13
6c1	-67.14	87.91	-93.35	1.00	-93.36	0.00	0.88	
6c2	-58.17	87.02	-84.10	0.00				
6d1	-65.51	87.87	-91.70	1.00	-91.70	1.65	0.05	
6d2	-57.45	87.42	-83.51	0.00				
7a1	12.70	90.31	-14.20	1.00	-14.20	3.92	0.00	
7a2	18.40	95.52	-10.06	0.00				
7b1	12.40	92.86	-15.26	1.00	-15.27	2.85	0.01	
7b2	17.92	92.98	-9.83	0.00				-17.93
7c1	11.60	97.47	-17.44	1.00	-17.45	0.67	0.24	
7c2	18.45	96.92	-9.83	0.00				
7d1	10.40	95.73	-18.11	1.00	-18.12	0.00	0.75	
7d2	17.69	92.05	-9.73	0.00				
8	35.23	85.41	9.78				1.00	9.78
9	25.67	89.88	-1.11				1.00	-1.11
10a	-5.87	91.35	-33.09				0.8	-32.93
10b	-4.86	92.01	-32.28				0.2	
11a	-58.15	105.38	-89.55				0.71	
11b	-56.43	102.66	-87.03				0.01	-89.35
11c	-58.46	102.46	-88.99				0.27	
11d	-56.43	102.84	-87.08				0.01	

Table- 3 The calculated tautomeric equilibrium constants of indoles in aqueous solution (ε = 78.4)

Tautomeric equilibrium	AM1			PM3		
	$\delta\Delta G_f$[a] (kcal/mol)	K_T[b]	pK_T[c]	$\delta\Delta G_f$[a] (kcal/mol)	K_T[b]	pK_T[c]
1a-1b	2.05	3.10×10^{-2}	1.51	3.36	3.40×10^{-3}	2.47
1a-1c	.45	6.20×10^{-18}	17.20	21.02	7.78×10^{-16}	15.10
1b-1c	21.40	1.99×10^{-16}	15.70	17.66	1.10×10^{-13}	12.96
2a-2b	2.19	2×10^{2}	1.70	2.91	7.29×10^{-3}	2.14
2a-2c	27.69	4.87×10^{-21}	20.31	26.61	3.01×10^{-20}	19.52
2a-2d	3.88	1.40×10^{-3}	2.85	9.20	1.78×10^{-7}	6.75
2b-2c	25.50	$.98\times 10^{-19}$	18.70	23.70	4.12×10^{-18}	17.38
2b-2d	1.69	6×10^{2}	1.24	6.28	2.44×10^{-5}	4.61
2c-2d	-23.80	2.92×10^{17}	-6×10^{-2}	-17.41	5.91×10^{12}	-12.77
3a1-3a2	2.41	1.7×10^{2}	1.77	3.97	1.21×10^{-3}	2.92
3b1-3b2	0.82	2.5×10^{1}	0.60	1.88	4.1×10^{2}	1.38
3c1-3c2	0.05	9.11×10^{-1}	0.04	4.49	5.5010^{-4}	3.26
3d1-3d2	2.86	7.9×10^{-3}	2.10	4.37	6.20×10^{-4}	3.21
4a1-4a2	44.31	3.12×10^{-33}	32.50	29.02	5.08×10^{-22}	21.29
4b1-4b2	25.58	1.71×10^{-19}	18.76	29.22	3.68×10^{-22}	21.43
5a1-5a2	4.64	3.90×10^{-4}	3.41	6.07	3.50×10^{-5}	4.45
5b1-5b2	90.72	2.81×10^{-67}	66.55	6.89	8.81×10^{-6}	4.05
5c1-5c2	4.67	3.74×10^{-4}	3.43	7.75	2.06×10^{-6}	4.05
5d1-5d2	5.90	4.69×10^{-5}	4.32	7.97	1.40×10^{-6}	5.85
6a1-6a2	5.50	9.20×10^{-5}	4.03	7.49	3.17×10^{-6}	5.50
6b1-6b2	3.78	1.68×10^{-5}	2.77	8.27	8.45×10^{-7}	6.07
6c1-6c2	7.07	6.48×10^{-6}	5.19	9.25	1.63×10^{-7}	6.79
6d1-6d2	5.54	8.60×10^{-5}	4.06	8.19	9.76×10^{-7}	6.01
7a1-7a2	3.77	1.71×10^{-3}	2.76	4.13	9.21×10^{-4}	3.03
7b1--7b2	2.53	1.39×10^{-2}	1.86	5.43	1.03×10^{-4}	3.99
7c1-7c2	3.10	5.30×10^{-3}	2.27	7.61	2.59×10^{-6}	5.58
7d1-7d2	5.82	5.30×10^{-5}	4.27	8.38	7.10×10^{-7}	6.15

a $\delta\Delta G_f = \Delta G_{f(b)} - \Delta G_{f(a)}$.

b $K_T = e^{(-\delta\Delta G / RT)}$ R = 1.987 × 10^{-3}kcal/mol and T = 298K.

c $p^{K}{}_{T} = -\log {}^{K}{}_{T}$

In AM1 calculations, compound **4** prefers *anti* (4a) from with preference of 100% and in PM3 calculations it prefers *anti* (4a) and *syn* (4b) forms with preference of 32 and 68%, respectively.

In AM1 calculations, compound **5** prefers *anti-syn* (5b) and *syn-syn* (5d) forms with preference of 25 and 75%, respectively. In PM3 calculations, it prefers *anti- anti* (5a), and *syn- syn* (5d) forms with preference of 79 and 21%, respectively.

In AM1 calculations, compound **6** prefers *syn-syn* (6d) form with preference of 90% and in PM3 calculations; it prefers *syn-anti* (6c) form with preference of 88%.

In AM1 calculations, compound **7** prefers *syn-syn* (7d) form with preference of 95% and in PM3 calcu -lations, it prefers *syn -syn* (7d), & *syn-anti* (7c) forms with preference of 75 and 24%, respectively.

In AM1 calculations, compound **10** prefers *syn* (10b) form with preference of 91% and in PM3 calcu lations it prefers *anti* (10a) and s*yn* (10b) forms with preference of 80 and 20%, respectively.

In AM1 calculations, compound **11** prefers *anti-syn* (11b) and *syn-syn* (11d) forms with preference of24 and 73%, respectively. In PM3 calculations, it prefers *anti-anti* (11a), and *syn-anti* (11c) forms with preference of 71 and 27%, respectively.

The AM1 and PM3 calculated tautomeric equilibrium constants K_T was calculated and are given in **Table-3**

CONCLUSIONS

The obtained results indicated that AM1/ COSMO and PM3/ COSMO solvation method is able to provide reasonable estimates of protomeric tautomerism for this type heterocycles in aqueous solution. The AM1 & PM3 calculations indicate that the compound **3** prefers *anti-anti* & *anti-anti* forms, **4** *anti*-, **5** *syn-syn*, **6** *syn-syn*, **7** *syn-syn*, **10** *syn* forms respectively over other tautomeric forms by different percentages.

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