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A theoretical study on isomerization process of hypocrellin A in ground state

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Abstract

The isomerization of hypocrellin A (HA), a naturally occurring perylenequinonoid photosensitizer, has aroused much interest in recent years, which comprises intramolecular H-atom transfer (IHT) and helix interconversion processes. Although much effort has been devoted to investigating the processes by means of various spectroscopy methodologies, there is no theoretical study on the isomerization of HA, because the molecule is too large to do high-level quantum chemical calculations. In this paper, a combined ab initio method RHF/6-31G(d,p)//AM1 was employed to calculate the ground-state-energies associated with the different isomers and the transition states for the IHT of HA. It was found that: (i) the most stable isomers for HA were the left-handed-4,9- or 3,10-quinones, in good agreement with the experimental findings; (ii) the barriers for four IHT processes are around 40 kJ/mol, very similar to the barriers for active center of HA, suggesting that the side chains of HA have little influence on the IHT barriers; and (iii) the dipole moments for the IHT transition states vary a little compared with those of the initial states, suggesting that the isomerization of HA in ground state will be slightly influenced by solvent polarity.

Keywords: Ab initio; AM1 method; Hypocrellin A; Intramolecular H-atom transfer; Isomerization; Perylenequinonoid derivatives

1. Introduction

Hypocrellin A (HA, Scheme 1) is a naturally occurring perylenequinonoid pigment (PQP), which has attracted much attention in recent years, owing to its excellent photosensitizing activity and interesting isomerization process [1–8]. As revealed by previous studies, HA undergoes intramolecular H-atom transfer (IHT) in ground state and excited state, which may be coupled with helix interconversion [9–11].

Much effort has been devoted to investigate the isomerization of HA and other PQPs. However, due to the complexity of the process, there exist many debates on this topic and therefore, theoretical investigation is needed to get deeper insight into the elusive phenomenon [12–22]. As HA contains tens of heavy atoms, most of the theoretical studies focused only on the active center of HA, namely, 4,9-dihydroxyl-3,10-perylenequinone. However, apparently, to have a

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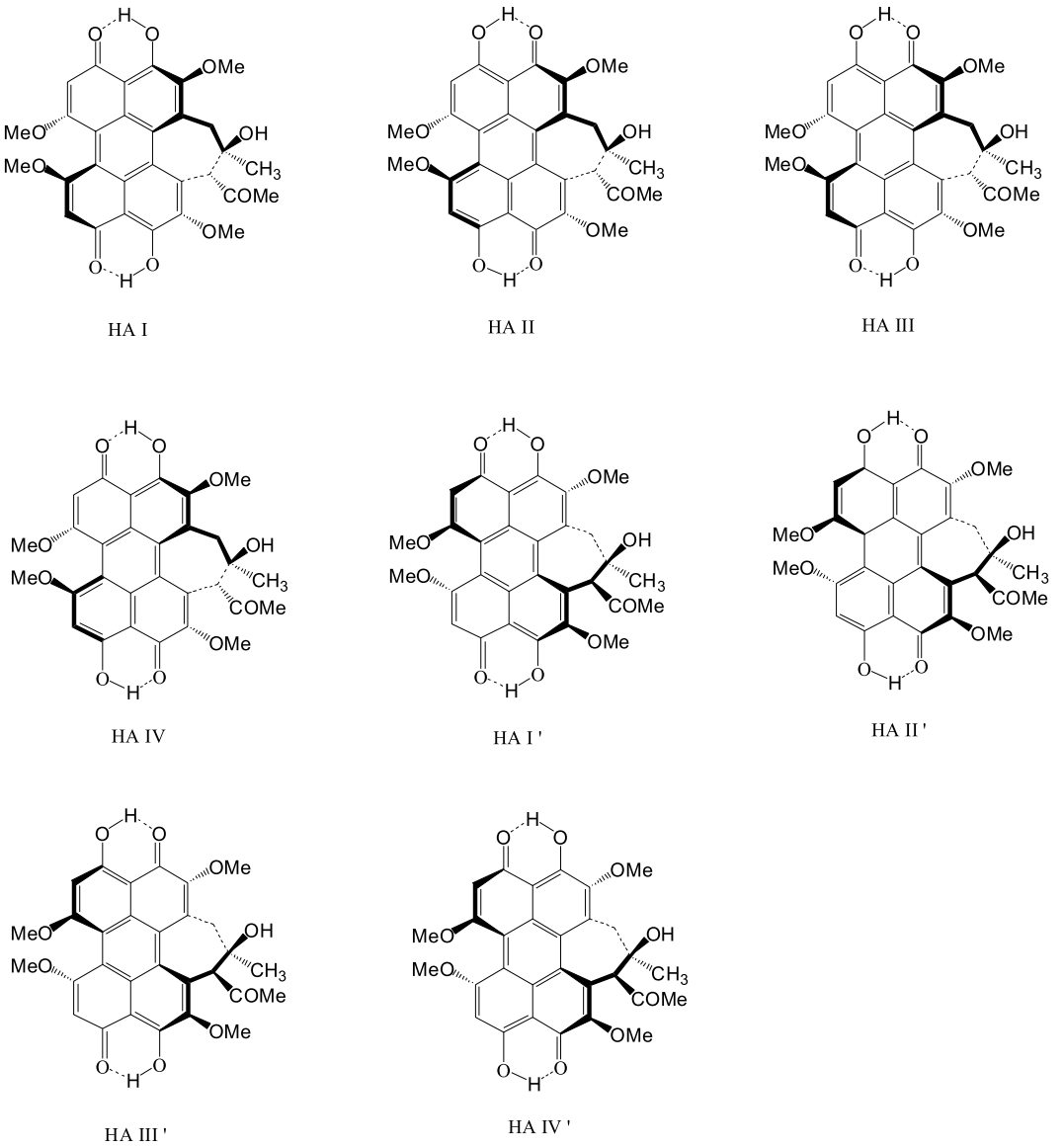


Scheme 1. Eight isomers of HA.

comprehensive understanding on the isomerization of HA, we have to study the whole molecule. Recently, it was proposed that a combined ab initio method took advantages of economy and accuracy, in which a semiempirical quantum chemical method, such as AM1, was used to optimize the molecular structure and then Hartree–Fock (HF) method was employed to calculate the single point energy (SPE) [22].

In this paper, we attempt to investigate the isomerization of HA by means of a combined ab initio method. The results will shed new light on the elusive isomerization of hypocrellins.

2. Methods

The molecular geometries were optimized, firstly, by molecular mechanic method, and then,

by semiempirical quantum chemical method AM1 [23]. Finally, restricted Hartree–Fock (RHF) functional on the basis set of 6-31G(d,p) was used to calculate the SPE in gas-phase at 298 K. The molecular energy consists of RHF/6-31G(d,p) calculated SPE and AM1 calculated zero point vibrational energy (ZPVE) and vibrational correction to the energy (scaled by a factor of 0.947). All located transition states exhibited the expected one normal imaginary frequency with a transition vector corresponding to the motion of atoms during the IHT process. The quantum chemical calculations were accomplished by Gaussian 94 program [24].

3. Results and discussion

3.1. Energy profile of isomers

Theoretically, HA has eight isomers (Scheme 1), with the enthalpy order: I < II < III < IV < I′ < II′ < IV′ < III′ (Table 1). It is interesting to find that the left-handed-helix isomers are more stable than the right-handed counterparts, consistent with the NMR observations [9,10]. On the other hand, the 4,9- or 3,10-quinones are more stable than the 3,9- or 4,10-quinones, which is in good agreement with the previous findings on the active center of hypocrellins [13] and can be understood through the Kekule-structure-count (*K* value) analysis proposed by Gutman et al. [25]. According to the resonance theory, the higher the *K* value, the more stable the molecule. As shown in Scheme 2, the *K* values for 4,9- or 3,10-quinones are indeed higher than those of 3,9- or 4,10-quinones.

In brief, the most stable isomers for HA are the left-handed-4,9- or 3,10-quinones, i.e., HA I and HA II. Hence, the following studies on IHT of HA will focus on the two isomers.

Table 1
Thermodynamic parameters for HA in initial state and transition state calculated by RHF/6-31G(d,p)//AM1

	TE (Hartree)[a]	TCE (Hartree)[b]	Enthalpy (Hartree)
HA I	−1899.785589	0.564944	−1899.235898
HA II	−1899.785712	0.565189	−1899.235783
HA III	−1899.778554	0.564945	−1899.228863
HA IV	−1899.778211	0.564986	−1899.228480
HA I′	−1899.776271	0.565244	−1899.226289
HA II′	−1899.773923	0.565460	−1899.223730
HA III′	−1899.765248	0.565292	−1899.215219
HA IV′	−1899.769969	0.565185	−1899.220044
TS 1	−1899.765655	0.559402	−1899.221357
TS 2	−1899.765651	0.559411	−1899.221344
TS 3	−1899.762725	0.559599	−1899.218235
TS 4	−1899.764916	0.559542	−1899.220482

[a] Total electronic energy.
[b] Thermal correction to energy.

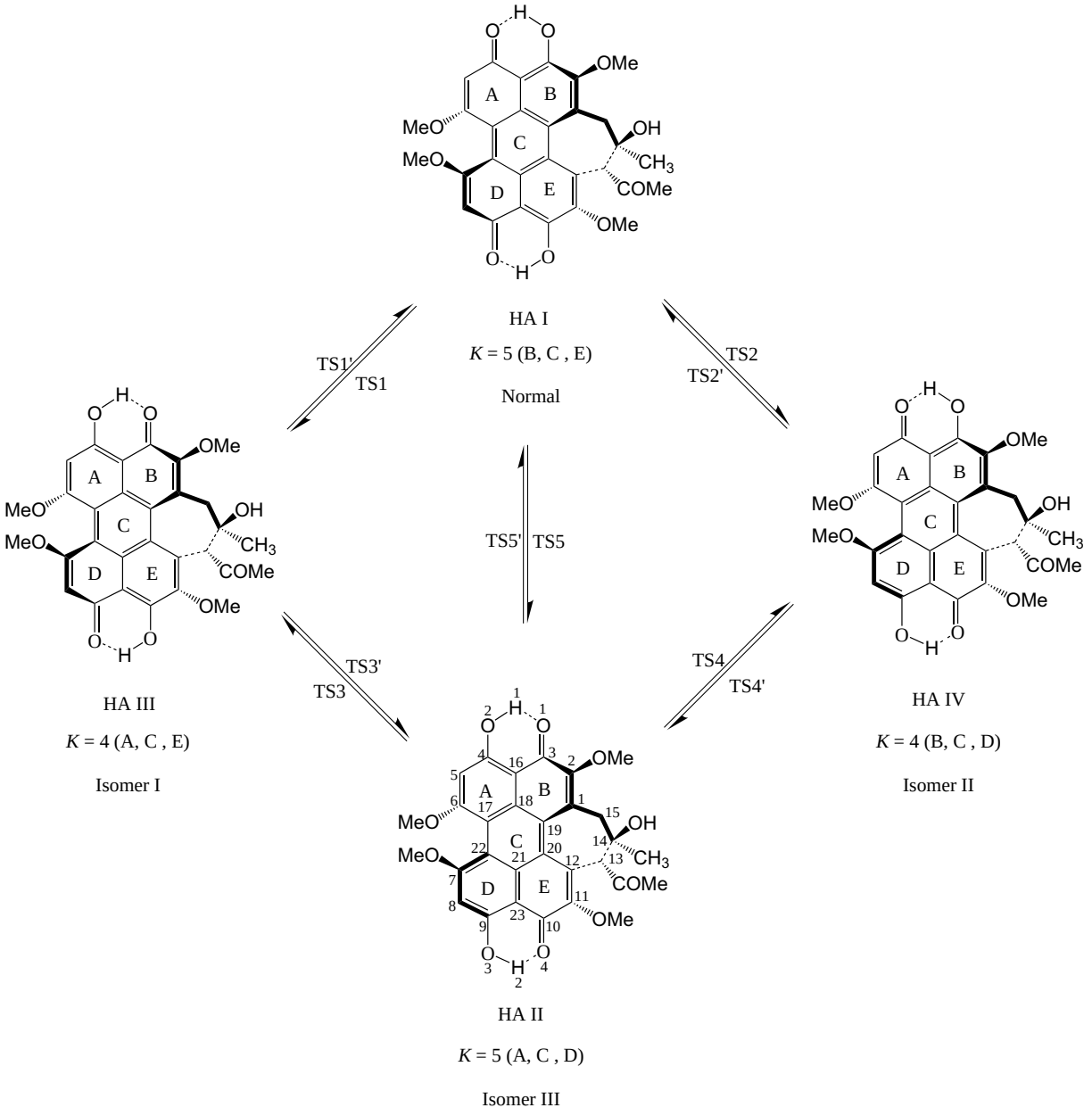
3.2. Barriers for transition states of IHT

Beginning from HA I and HA II, there exist five kinds of IHT processes and transition states (TS1–TS5, Scheme 2), in which TS1–TS4 are for single proton transfer, while TS5 is for a double proton transfer. As previous studies indicated the activation energy for double proton transfer would be much higher than that of single proton transfer and thus, would be forbidden in view of kinetics [14]. So, only barriers for TS1–TS4 were calculated and listed in Table 1.

It is interesting to notice that the barriers for four TSs of HA are around 40 kJ/mol, close to the barriers for hypericin (HYP) and active center of HA and hypomycin B (HMB) (Table 2) [12,21,22], suggesting that the side chains of HA have little influence on the IHT barriers and the IHTs pertaining to the H1 and H2 are similar to each other. This is also consistent with the conclusion drawn on HMB [22]. Accordingly, it is reasonable to consider that the IHT barrier of active center of HA in excited state is also similar to that of parent HA. However, the experimentally determined IHT barrier for HA in excited state is 1.72 ± 0.37 kJ/mol [8], much lower than the calculated value for active center of HA, 10.38 kJ/mol [21]. Hence, it seems that further experimental study and higher-level theoretical calculations are needed to get a comprehensive understanding on the IHT of HA in excited state.

3.3. Charge variance in the isomerization process

It has been found that the IHT barriers of PQPs are mainly determined by the change of the charge



Scheme 2. Isomerization of left-handed HA. *K* is the Kekule-structure-count. The letters in parentheses indicate the domains of cyclic conjugation.

on transferred proton [16]. The higher the charge increment on proton, the higher the barrier. From Table 3, it can be seen that when H1 is transferred, the charge on H1 varied greatly, however, the charge on H2 changed a little. A reverse phenomenon can be observed for H2 transfer, in accordance with the independent IHT mode proposed for the active center of HA.

Table 2
IHT barriers (kJ/mol) for HA calculated by RHF/6-31G(d,p)//AM1

	TS1 (TS1′)	TS2 (TS2′)	TS3 (TS3′)	TS4 (TS4′)	HA[a]	HMB[b]	HYP[c]
Barriers	38.18 (19.71)	38.21 (18.74)	46.07 (27.90)	40.17 (21.00)	37.83	36.51	41.00–48.12

[a] Barrier for active center of HA calculated by RHF/6-31G [21].
[b] Barrier for active center of HMB calculated by RHF/6-31G(d,p) [22].
[c] Barrier for HYP calculated by MP2/6-31G(d)/RHF/3-21G [12].

Table 3
Charges on hydrogen atoms of HA in different states calculated by RHF/6-31G(d,p)//AM1

	HA I	HA II	HA III	HA IV	TS1	TS2	TS3	TS4
H1	0.4081	0.4070	0.4102	0.4109	0.5367	0.4088	0.4073	0.5363
H2	0.4094	0.4057	0.4123	0.4091	0.4102	0.5374	0.5367	0.4065

Table 4
Dipole moments (in Debye) of HA in different states calculated by RHF/6-31G(d,p)//AM1

	HA I	HA II	HA III	HA IV	TS1	TS2	TS3	TS4
Dipole moment	5.3087	6.4221	6.1330	5.8177	6.0304	6.2652	6.6485	5.8410

3.4. Dipole moment variance in the isomerization process

As shown in Table 4, the dipole moments for different isomers of HA are similar to one another and the dipole moments for the transition states vary a little compared with those of the initial states, suggesting that the isomerization of HA in ground state will be slightly influenced by solvent polarity. Moreover, it is interesting to notice that the dipole moment value of HA is much higher than that of active center of HA (that is near to zero) [15,21], which should arise from the fact that the good symmetry in the active center is disrupted by the side chains of HA. However, it is anticipated that the dipole moment will change dramatically in the isomerization of excited state, because an evident solvent polarity-dependence of IHT rates of HA has been observed by experimental study [26].

In brief, the combined ab initio method predicts correctly the left-handed-4,9- or 3,10-quinones are the most stable isomers for HA. And the calculation indicates that the side chains in HA have little influence on the isomerization barriers. The success of the method suggests that it is also applicable to study the isomerization of other PQPs.

Acknowledgements

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