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Short Communication

Theoretical study on intramolecular hydrogen transfer involving amino-substituted perylenequinone

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Abstract

2-Amino-perylenequinone (2-NH_2-PQ) and 3,10-diamino-perylenequinone (3,10-diNH_2-PQ) were used as model compounds for investigating the intramolecular hydrogen transfer (IHT) reactions involving amino-substituted perylenequinonoid photosensitizers (PQP). A semi-empirical MO method (AM1) was employed to calculate the theoretical values associated with the IHT process. It was found that amino-substitution enhanced the entropy of a specific isomer of PQ, causing it to be more stable than other possible isomers. Amino-substitution raised the HOMO energy levels (E_{HOMO}) of PQ, by increasing its electron-donating ability. It was also found that placing an NH_2 group in the 2-position lowered the energy barriers to IHT in PQ in the ground state and the singlet excited state, and 3,10-diNH_2-substitution increased the IHT energy barriers in PQ in both states. The energy barrier for the double IHT was almost two times the energy barrier for the single IHT, making the double IHT a less important process. The IHT energy barrier for NH_2-PQ decreased in the singlet excited state, while the energy barrier decrease from the excited state to ground state was larger for 2-NH_2-PQ than for 3,10-diNH_2-PQ. The charge on the hydrogen atom and the molecular dipole moment varied during the IHT process, and the IHT energy barriers were governed by the differences in the charges on the hydrogen atom in the transition state and initial state. The dipole moment for the molecular singlet excited state changed considerably during the IHT process, indicting that IHT would be accelerated by strongly polar solvents. Like the PQ case, there was no correlation between changes in the charge on the hydrogen atom and dipole moment changes in the IHT process. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: AM1 method; Amino-substituted perylenequinonoid photosensitizer; Intramolecular hydrogen transfer; Amino-substituted perylenequinone; Perylenequinonoid photosensitizer

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1. Introduction

Perylenequinonoid photosensitizers (PQP), such as hypericin (HYP), hypocrellin A (HA), and hypocrellin B (HB), are naturally occurring

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pigments that have attracted much attention due to their excellent photosensitizing properties [1–7]. To enhance the absorption of PQP in the region of therapeutic utility (600–900 nm), amino-substituted PQP derivatives have been synthesized [8–12]. Biological testing showed that the amino-PQP derivatives have a much higher photopotentiation factor than the parent PQP, viz. more than 200 versus 4 at a 4 J cm^{-2} dose of red light [12,13]. Hence, amino-PQP derivatives hold promise as new agents for photodynamic therapy.

Heretofore, amino-PQP compounds have included at least two types of derivatives, viz. 2-amino-PQP and 3,10-diamino-PQP [8–12]. Using HB as an example, it can be seen from Scheme 1 that both amino-PQP structures possess intramolecular hydrogen bonding, and consequently preserve the intramolecular hydrogen transfer (IHT) process. This is important because it has been shown that IHT is responsible for the high photosensitizing activity of PQP, and that IHT facilitates the intersystem crossing of PQP from the singlet excited state to triplet excited state. Further IHT enhances the triplet excited state quantum yield of PQP [14].

Since IHT is a well-known and important process [15], the IHT of PQP has been studied experimentally and via theoretical calculations [16–32]. Interestingly, however, the IHT of amino-PQP has not been investigated. Given that 3,10-dihydroxy-4,9-perylenequinone (PQ) (Scheme 2) is the active center for PQP [33–36], two NH$_2$-substituted PQ structures, 2-NH$_2$-PQ (Scheme 3) and 3,10-diNH$_2$-PQ (Scheme 4) were employed as model compounds for investigating the IHT process. It was anticipated that the results would aid our understanding of the IHT of various amino-PQP molecules.

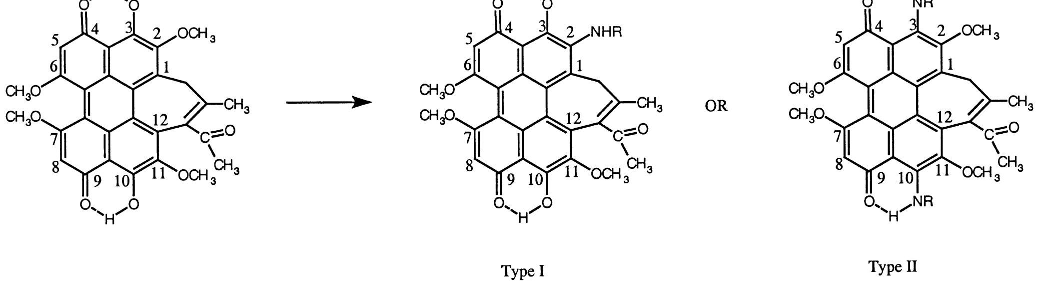
2. Methods

PQ, 2-NH$_2$-PQ, and 3,10-diNH$_2$-PQ structures were optimized using the molecular mechanics method (MMX) [37] in the PCMODEL program, and the resultant structures were optimized using a semi-empirical MO method (AM1) [38] in the HYPERCHEM program. The root-mean-square (RMS) was set at 0.01 kcal/mol and the thermodynamic parameters were calculated using AM1 in the MOPAC 7.0 program. Since these molecules are planar, only one parameter, the O13–H17 distance, was used as reaction coordinate in determining the transition state via the TS method in MOPAC 7.0.

3. Results and discussion

3.1. Studies involving the stability of PQ, 2-NH$_2$-PQ, and 3,10-diNH$_2$-PQ isomers

Results from calculating the thermodynamic parameters for PQ, 2-NH$_2$-PQ, and 3,10-diNH$_2$-PQ isomers are summarized in Table 1. It is well known that the lower the free energy, the more stable the molecule. This means that the PQ isomer **IV** is more stable than isomer **III**. However, the 2-NH$_2$-PQ isomer **V** and the 3,10-diNH$_2$-PQ isomer **IX** is more stable than corresponding isomers. Furthermore, it is interesting to note that the higher stability of structures **IV**, **V**, and **IX** is



Scheme 1. Hypocrellin B and its amino-substituted derivatives. Type I, 2-amino-hypocrellin B; Type II, 3, 10-diamino-hypocrellin B.

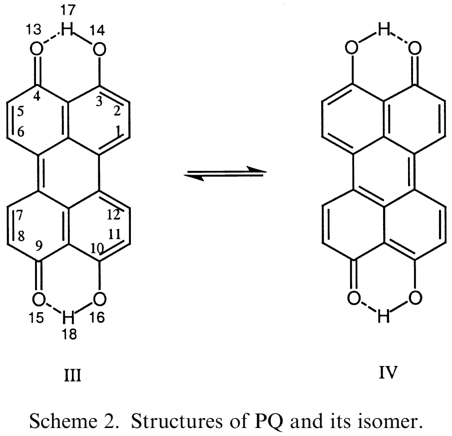
influenced more by molecular entropy than by enthalpy.

Theoretically, the 2-amino-hypocrellins have isomers that correspond to the four isomers of 2-NH_2-PQ. Experimentally, however, only the structure **I** was observed [8–10]. Similarly, only the structure corresponding to isomer **IX** of 3,10-diNH_2-PQ was observed experimentally for 3,10-amino-hypocrellins [11,13].

From a study of the HOMO energy levels (E_{HOMO}) of these compounds, it can be determined that NH_2-PQ is more electron-rich than PQ. This is significant because electron-rich amino-hypocrellins give a higher quantum yield of superoxide anion, produced after electron transfer from amino-hypocrellins to oxygen, than the parent hypocrellins [8,9].

3.2. Energy barriers for IHT in NH_2-PQ molecules

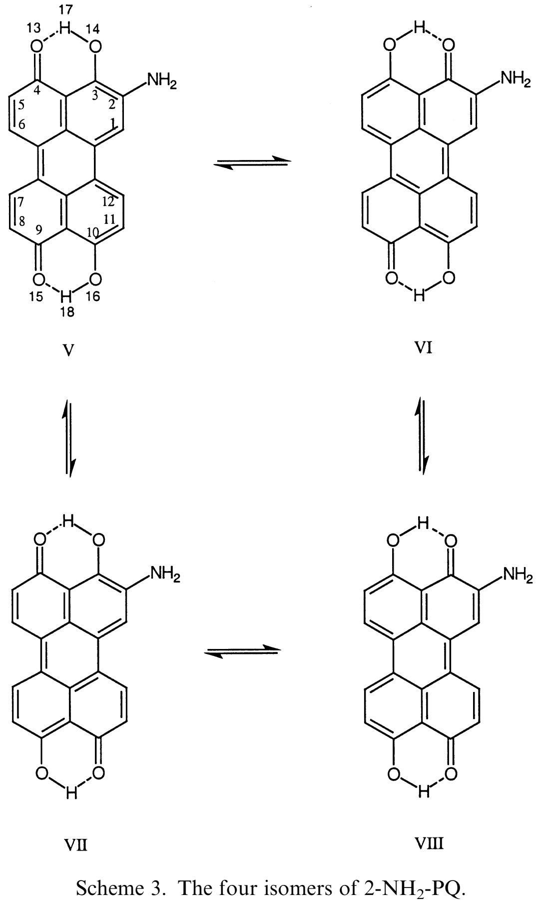
Although there are various possible IHT pathways for NH_2-PQ, only the one associated with the most stable structure (**V**) was investigated. The heats of formation for the different states of NH_2-PQ were calculated (Tables 2 and 3), and the results were used to determine the energy barrier for IHT. When the reaction coordinate (O13–H17 distance) was varied, the heats of formation changed (Figs. 1 and 2). The largest heat of formation for the IHT process corresponded to the transition state for IHT.



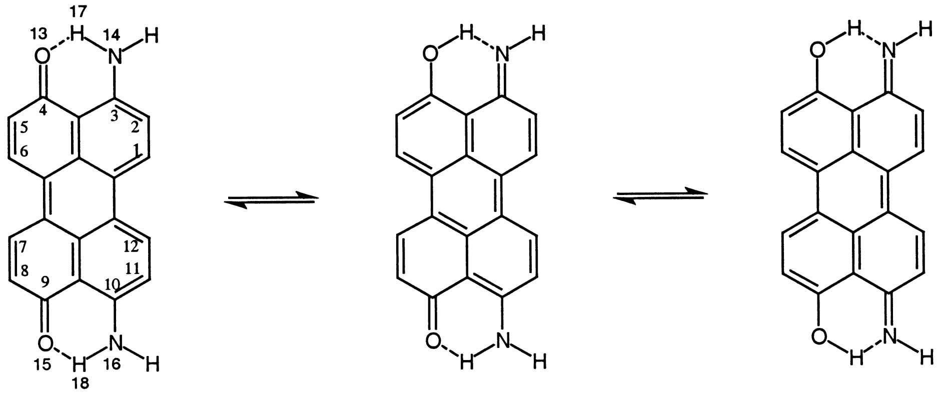
Scheme 2. Structures of PQ and its isomer.

Theoretically, there are two types of IHT process for NH_2-PQ compounds, the single IHT (**V**→**VI**), and the double IHT (**V**→**VIII** and **IX**→**XI**) for 2-NH_2-PQ and 3,10-diNH_2-PQ, respectively. From Table 2, it can be seen that the energy barrier for the double IHT is nearly twice that for the single IHT. Therefore, there is a weak synergistic effect in the double IHT, causing the rate of double IHT to be much slower than that of the single IHT. This means that the double IHT process is less important in NH_2-PQ compounds.

The energy barriers for the single IHT process for 2-NH_2-PQ in the ground state and singlet excited state are lower than that of parent compound (PQ), and the energy barrier for **V**→**VI** is lower than that for **V**→**VII** (Table 2), suggesting that NH_2-substitution facilitates IHT in PQ and that the hydrogen atom on the OH-group adjacent



Scheme 3. The four isomers of 2-NH_2-PQ.



IX X XI

Scheme 4. The three isomers of 3,10-diNH$_2$-PQ.

Table 1
Thermodynamic parameters for PQ, 2-NH$_2$-PQ, and 3,10-diNH$_2$-PQ (300 K)

	PQ		2-NH$_2$-PQ				3,10-diNH$_2$-PQ		
	III	**IV**	**V**	**VI**	**VII**	**VIII**	**IX**	**X**	**XI**
Enthalpy (cal/mol)	10,739.20	10,797.53	11,631.45	11,499.07	11,537.85	11,504.55	11,138.16	10,851.64	10,859.07
Entropy (cal/mol) (cal/mol K)	125.71	126.69	131.58	130.24	130.58	130.52	129.87	126.88	127.27
Free energy (cal/mol)	−26,973.80	−27,209.47	−27,842.55	−27,572.93	−27,636.15	−27,651.45	−27,822.84	−27,212.36	−27,321.93
E_{HOMO} (eV)[a]	−8.9010	−8.5418	−8.5242	−8.1046	−8.4084	−8.4241	−8.0539	−7.9480	−8.4527

[a] HOMO energy level.

Table 2
Heats of formation and IHT energy barriers for 2-NH$_2$-PQ and PQ (kcal/mol)

	Ground state	Singlet excited state
Isomer **V**	−57.94	19.48
Transition state for **V**→**VI**	−37.92	29.48
Isomer **VI**	−57.40	11.89
Transition state for **V**→**VII**	−37.26	30.42
Isomer **VII**	−54.96	17.10
Transition state for **V**→**VIII**	−19.01	48.45
Isomer **VIII**	−60.60	16.42
Energy barrier for **V**→**VI**	20.02	10.00
Energy barrier for **V**→**VII**	20.68	10.94
Energy barrier for **V**→**VIII**	38.93	28.97
Energy barrier for single IHT of PQ [30]	21.45	13.24

Table 3
Heats of formation and IHT energy barriers for 3,10-diNH$_2$-PQ (kcal/mol)

	Ground state	Singlet excited state
Isomer **IX**	27.46	93.54
Transition state of **IX**→**X**	56.29	120.04
Isomer **X**	42.19	109.72
Transition state of **X**→**XI**	82.71	144.60
Isomer **XI**	50.91	135.58
Energy barrier for single IHT	28.83	26.50
Energy barrier for double IHT	55.25	51.06

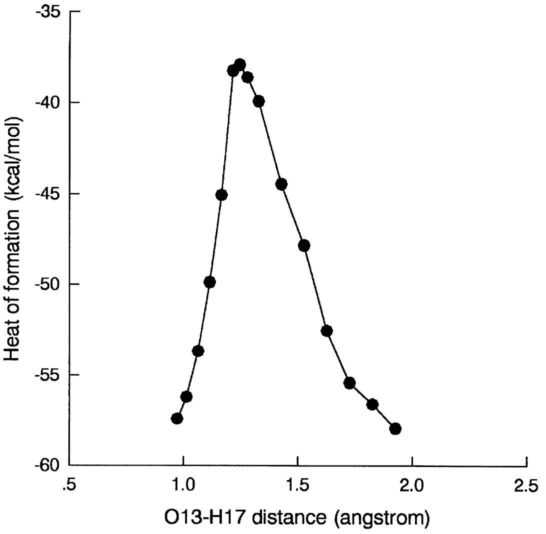


Fig. 1. Relationship between heat of formation and H-bonding distance for 2-NH_2-PQ.

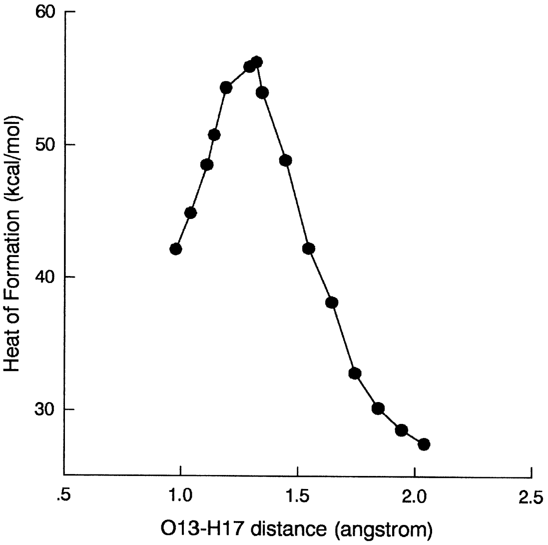


Fig. 2. Relationship between heat of formation and H-bonding distance for 3,10-diNH_2-PQ.

to the NH_2 group transfers faster. The energy barriers for the single IHT process in 3,10-diNH_2-PQ, i.e. **IX→X**, is higher than that of PQ (**III→IV**) and 2-NH_2-PQ (**V→VI**), indicating that **IX→X** will be slower than **III→IV** and **V→VI**.

The energy barriers for the single IHT in PQ, 2-NH_2-PQ, and 3,10-diNH_2-PQ in the singlet excited state are much lower than those in the ground state (Table 3). These results arise from the fact that the acidities of the O–H and N–H groups increase and the basicity of keto increase in singlet excited state. Since the acidity of the O–H group increases faster than that of the N–H group [39], the energy barrier-decrease for the excited state to ground state transition is larger for 2-NH_2-PQ than for 3,10-diNH_2-PQ.

3.3. Atomic charges and dipole moments in the IHT process

The results of a previous study showed that the IHT energy barrier for PQ was mainly determined by changes in the charge on H-17 [32]. Similarly, the results in Table 4 and Figs. 3 and 4 show that, for NH_2-PQ, the charges on O13, O14, and H17 varied greatly during the IHT process. The charge on H-17 increased approximately 30% at the transition state, compared to the initial value and it is a reflection of the IHT barrier for the corresponding states. For instance, the charge difference on the H-atom of 2-NH_2-PQ in the ground state was higher than that in the excited state, which is consistent with the fact that the former has a higher IHT energy barrier than the latter. However, the charge on H-18 changed a little during the H-17 transfer process (**V→VI**). This is in agreement with a weak synergistic effect on the double IHT.

In the IHT process, the molecular dipole moment also varied (Table 5). The dipole moment changed significantly during IHT in the excited state, indicating that IHT is favored by highly polar solvents. This is consistent with the IHT of PQ [18,21,31] and should be observed experimentally. On the other hand, the dipole moment changed slightly during IHT of ground state molecules. This indicates that IHT in the ground state will be affected little by polar solvents. Similar to PQ, there was no correlation between dipole moment changes and changes in H-atom charge. Although the charge differences on the H-atom were higher in the ground state than in excited state, the changes in dipole moment were much

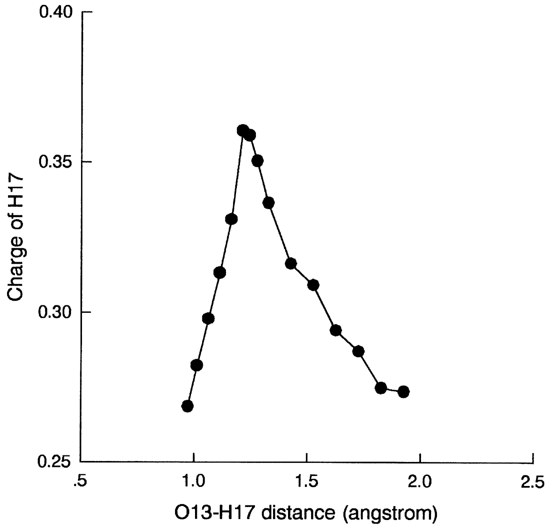


Fig. 3. Relationship between charge on H-17 and H-bonding distance for 2-NH_2-PQ.

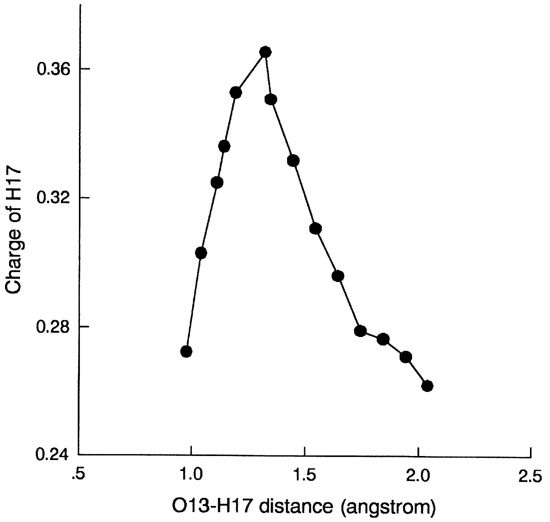


Fig. 4. Relationship between charge on H-17 and H-bonding distance for 3,10-diNH_2-PQ.

Table 4
Charges on H and O for single IHT of 2-NH_2-PQ and 3,10-diNH_2-PQ

	Isomer V (**IX**)				IHT transition state				Isomer VI (**X**)				CD[c]
	O13	H17	H18	O(N)14	O13	H17	H18	O(N)14	O13	H17	H18	O(N)14	
Ground state[a]	−0.3382	0.2736	0.2691	−0.2688	−0.3536	0.3589	0.2708	−0.3772	−0.2495	0.2686	0.2732	−0.3563	0.0853
Singlet excited state[a]	−0.3871	0.2879	0.2691	−0.2795	−0.3538	0.3523	0.2701	−0.4116	−0.2420	0.2662	0.2682	−0.3813	0.0644
Ground state[b]	−0.3540	0.2621	0.2621	−0.3619	−0.3681	0.3655	0.2682	−0.3962	−0.2560	0.2724	0.2707	−0.3071	0.1034
Singlet excited state[b]	−0.3669	0.2782	0.2797	−0.3252	−0.3502	0.3714	0.2733	−0.3963	−0.2512	0.2757	0.2702	−0.2844	0.0932

[a] Data for 2-NH_2-PQ.

[b] Data for 3,10-diNH_2-PQ.

[c] Charge difference of H17 between IHT transition state and initial state.

Table 5
Dipole moments for single IHT of 2-NH_2-PQ and 3,10-diNH_2-PQ (D)

	Isomer V (**IX**)	IHT transition state	Isomer VI (**X**)
Ground state[a]	2.099	2.005	2.676
Singlet excited state[a]	4.182	5.202	2.360
Ground state[b]	4.345	4.237	4.132
Singlet excited state[b]	3.922	5.213	3.373

[a] Data for 2-NH_2-PQ.

[b] Data for 3,10-diNH_2-PQ.

lower in the former state. This arises from the fact that the dipole moment is determined not only by H-atom charge, but also by the charges on other atoms.

4. Conclusion

Amino-substitution influences the stability of PQ and changes its IHT process. Substitution of an NH_2 group in the 2-position lowers the IHT barrier, while 3,10-diNH_2-substitution enhances the IHT energy barrier. The IHT energy barrier for NH_2-PQ decreased in the singlet excited state. The IHT energy barrier is governed mainly by the changes in H-atom charge during the IHT process. However, the changes in dipole moment are not influenced by changes in the charges on the hydrogen atoms.

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