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Mechanism for intramolecular proton transfer involving hypericin

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Abstract

This paper pertains to the characterization of the transient species arising from intramolecular proton transfer involving hypericin. In this regard, a calculation showed that the dipole moment for the transition state associated with proton transfer was 11.63 D, which was much higher than the value (3.49 D) for the ground state. This suggests that a charge separation process such as proton dissociation or electron transfer is involved in the formation of the transient species. © 2000 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Hypericin (HYP; Fig.1; **1**) is a naturally occurring polycyclic quinonoid pigment that has received considerable attention, owing to its excellent photosensitization properties and its ability to deactivate the human immunodeficiency virus (HIV) [1–3]. Recently, much attention has been given to its intramolecular proton transfer (IPT) process [4–14], because of its importance in elucidating the photosensitization mechanism associated with HYP, and its utility as a model for verifying existing explanations pertaining to the IPT process.

It was reported that optical excitation of HYP produced a transient species having an absorption between 580 and 650 nm [5]. While, this species has been attributed to an IPT-generated tautomer of HYP (Fig. 1; **2**) [5,6,9–11] and to an intermediate tautomer [12,13], there are several observations to be explained before the transient species arising from IPT is established. These observations include: i. The absorption and fluorescence spectra of HYP exhibit good symmetry [5,6], which differs from the spectra of other molecules that also possess IPT, such as 3-hydroxyflavone [15] and 2-(2-hydroxyphenyl)benzothiazole [16]. ii. There is no deuterium isotope effect associated with the IPT of HYP. Instead, HYP and its deuterated form have identical proton transfer rates [5]. This is difficult to understand, since deuteration lowers the transfer rate in most of the IPT processes reported to date [17–19]. iii. The IPT barrier for HYP in the excited state is only 0.044±0.008 kcal/mol [14]. As the calculated barrier of IPT for HYP in the ground state is approximately 8 kcal/mol [20], the excited-state

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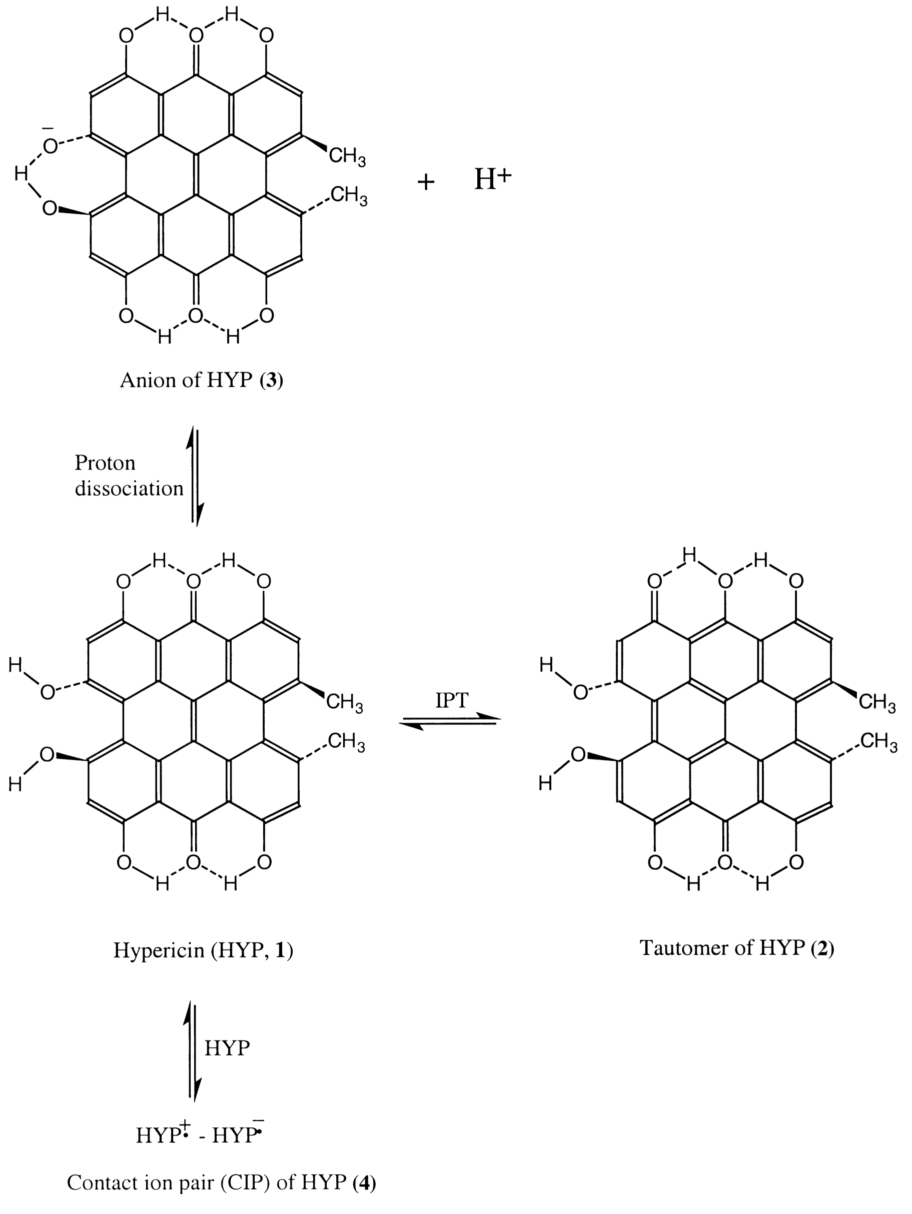


Fig. 1. HYP and the possible processes responsible for the formation of the transient species.

barrier seems unreasonably low. Although this abnormally low barrier was interpreted as arising from the fact that proton transfer lies within the adiabatic limit [14], it is still an unresolved point in view of the IPT barrier for 9-hydroxyphenalenone (9-HPO) [17]. In the case of 9-HPO, proton transfer occurs over an O–O distance of 0.2486 nm [21], which is very similar to that in HYP [20]. This value also lies in the adiabatic range, while the IPT barrier for 9-HPO in excited state is 6.44±2.29 kcal/mol [17], much higher than that of HYP.

It is clear that further studies are needed in order to understand the IPT of HYP. Since both a solvent polarity dependence for the IPT [6] and a relationship between chemical reaction rate and solvent polarity have been established [22], it is possible to calculate the dipole moment for the associated transition state. It is anticipated that the results would enhance our understanding of this process, and would be helpful in determining whether the transient species is due to IPT.

Since the time scales for IPT and the orientation of solvent dipoles have the same magnitude, it is assumed that the Gibbs free energy for the ground state and excited state of HYP, in a continuous medium of dielectric constant ϵ_r, is comparable to the Gibbs free energy in a similar medium having $\epsilon_r = 1$ [22]. This is determined from Eq. (1):

$$\varDelta G_{\text{solv}} = -(N_0/4\pi\varepsilon_0) \times \left(\mu^2/r^3\right) \times [(\varepsilon_r - 1)/(2\varepsilon_r + 1)] \tag{1}$$

where μ is the dipole moment, r is the radius of the pigments, ε_0 is the vacuum permittivity, and N_0 is the Avogadro constant. Thus, based on Eq. (1), a relationship between the IPT rate in polar solvents (ε_r) and non-polar solvents ($\varepsilon_r = 1$) can be obtained from kinetic analysis.

From transition state theory, one gets Eqs. (2) and (3):

$$\ln k = \ln A + \left(-\varDelta G^0_{\neq,\text{p}}/RT\right) \tag{2}$$

and

$$\ln k_0 = \ln A + \left(-\varDelta G^0_{\neq,\text{n}}/RT\right) \tag{3}$$

where k is the rate constant for IPT in polar solvents, k_0 is the rate constant for IPT in non-polar solvents, A is a constant, $\Delta G^0_{\neq,\text{p}}$ is the activation free energy in polar solvents, and $\Delta G^0_{\neq,\text{n}}$ is the activation free energy in non-polar solvents. Combining Eq. (2) with Eq. (3), we obtain Eq. (4):

$$\ln k = \ln k_0 + \left(\varDelta G^0_{\neq,\text{n}} - \varDelta G^0_{\neq,\text{p}}\right)/RT \tag{4}$$

From the relationship between $\Delta G^0_{\neq,\text{n}}$, $\Delta G^0_{\neq,\text{p}}$, ΔG_0, and $\Delta G_{\neq}$, expressed in Scheme 1, $\Delta G^0_{\neq,\text{n}} - \Delta G^0_{\neq,\text{p}} \approx \Delta G_0 - \Delta G_{\neq}$. This leads to Eq. (5):

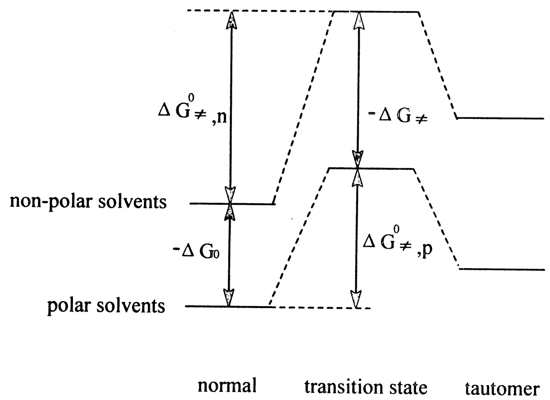
$$\ln k = \ln k_0 + \left(\Delta G_0 - \Delta G_{\neq}\right)/RT \tag{5}$$

where ΔG_0 is the relative Gibbs free energy of the pigments in the ground state and $\Delta G_{\neq}$ is the relative Gibbs free energy of the pigments in the excited state. Substituting Eq. (1) into Eq. (5) gives Eq. (6):

$$\ln k = \ln k_0 + \left[N_0\left(\mu^2_{\neq} - \mu^2_0\right)/4\pi\varepsilon_0 r^3 RT\right] \times [(\varepsilon_r - 1)/(2\varepsilon_r + 1)] \tag{6}$$

Therefore, a linear relationship between $\ln k$ and $(\varepsilon_r - 1)/(2\varepsilon_r + 1)$ is observed. Employing the IPT rates for HYP, $\mu^2_{\neq} - \mu^2_0$ can be obtained. In this approach, quantum tunnelling of hydrogen atoms was not considered, because the barrier for IPT was very small, and IPT is mainly a thermodynamic process.

The experimentally determined IPT rate constants for HYP in different solvents are listed in Table 1, and the relationship between $\ln k$ and $(\varepsilon_r - 1)/(2\varepsilon_r + 1)$ is shown in Fig. 2. In order to simplify the solvent effects, only the data determined in alcohols are used [6]. The $\mu^2_{\neq} - \mu^2_0$ was calculated to be 1.367×10^{-57} C^2 m^2, with $r = 0.6$ nm, $T = 295$ K. Due to the symmetry of the HYP molecule, μ^2_0 will be rather small. In fact, an AM1 [23] quantum calculation on the excited state of HYP indicates that μ_0 is 3.49 D. Thus, the calculated μ is 11.63 D, much higher than μ_0. This suggests that the dipole moment of the transition state increases markedly during the formation of the transient species. Since IPT induces only a rather small dipole



Scheme 1. Gibbs free energy diagram for IPT in polar and non-polar solvents.

Table 1
Experimental data for the IPT of HYP

	ε_r[a]	$(\varepsilon_r-1)/(2\varepsilon_r+1)$	τ[b] (ps)	k[c] (s^{-1})	ln k
Ethylene glycol	37.7	0.4804	6.4	1.56×10^{11}	25.77
Methanol	32.66	0.4774	6.7	1.49×10^{11}	25.73
Butanol	17.51	0.4584	11.0	9.09×10^{10}	25.23
Octanol	10.3	0.4306	12.6	7.94×10^{10}	25.10

[a] Dielectric constants for different solvents [22].
[b] Time scale for IPT [6].
[c] Rate constant for IPT.

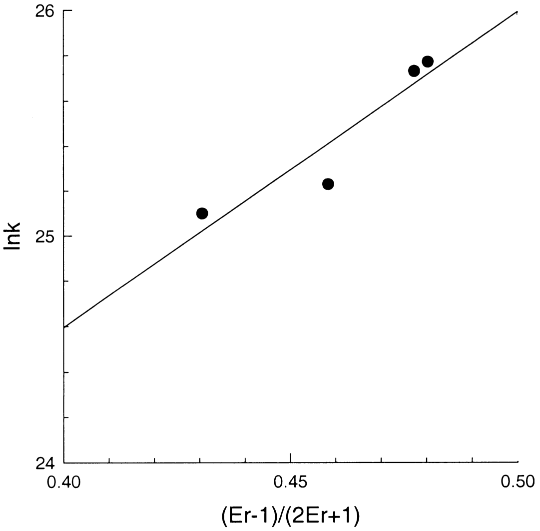


Fig. 2. Linear correlationship between the lnk of IPT for HYP and $(\varepsilon_r-1)/(2\varepsilon_r+1)$ ($r=0.9349$).

moment increase in perylenequinone, the active center of HYP [24], it is difficult to understand the abnormally high $\mu_{\neq}$. In view of the three above mentioned points, it is reasonable to suggest that the transient species does not arise from IPT, but instead arises from charge separation processes, such as proton dissociation or electron transfer.

It has been suggested that the transient species is simply an anion of HYP (Fig. 1, **3**), which has been observed in its crystalline state [25] and also has been the subject of theoretical studies [26]. Anion formation has been proposed to explain the symmetry between the absorption and fluorescence spectra of HYP [20]. In this case, the absorption and fluorescence of the transient species are in the 580–650 nm region, which is consistent with the corresponding spectra for the HYP anion [27]. Furthermore, the high μ can be attributed to proton dissociation, since this can cause a large dipole moment increase. However, this explanation does not account for the absence of a deuterium isotope effect and the abnormally low IPT barrier. Hence, electron transfer must be considered.

In the case of electron transfer, a contact ion pair (CIP) of HYP can be proposed to account for the transient species (Fig. 1, **4**). This would address most of the concerns regarding the HYP anion proposal. For instance:

i. The formation of CIP does not influence the steady-state spectra.
ii. A deuterium isotope effect would not be observed in CIP formation.
iii. Usually, the barrier for CIP formation is very low.
iv. The high μ would arise from the charge separation process.

In addition, the time scale for CIP formation is several ps, very similar to that for forming the transient species [5]. Most importantly, HYP has been shown to be a unique amphi-electronic pigment. It can either accept or donate an electron, depending on the presence of substrates in the system [28]. Therefore, it could form a charge transfer complex with a planar molecule, such as itself. On the other hand, it is difficult to explain why CIP formation does not correlate with solvent viscosity [6]. This means that there is no completely self-consistent model that accounts for all observations, which makes the nature of the photophysics of HYP uncertain but very interesting.

2. Conclusions

It is clear that the calculated dipole moment for the proton transfer transition state for excited HYP is so large that the mechanism previously proposed to account for the transient species is questionable. It is also clear that charge separation processes such as proton dissociation or electron transfer are involved in the formation of the transient species.

Acknowledgements

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