7-Azaindole-Assisted Lactam−Lactim Tautomerization via Excited-State Double Proton Transfer

Pi-Tai Chou,*,† Ching-Yen Wei,† Chen-Pin Chang,‡ and Chieng-Hwa Chiu‡

Departments of Chemistry
National Chung Cheng University, Chia-Yi, Taiwan, ROC
Fu Jen Catholic University, Shin Chuang, Taiwan, ROC
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The photophysics of 7-azaindole (7AI) have been studied extensively[1−25] since Taylor et al.[1] first reported the excited-state double proton transfer (ESDPT) in the 7AI dimer. The current topic of ESDPT in a variety of 7AI hydrogen-bonded complexes has important applications for probing both solvation dynamics and biological systems.[9−25] The ESDPT reaction in 7AI hydrogen-bonded systems can be classified into two categories. The acid, alcohol, and water assisted ESDPT in 7AI can be specified as a **catalytic** process since the molecular structure of the guest species (e.g., acetic acid in the acetic acid/7AI complex) remains unchanged (Figure 1a[26]). On the other hand, adiabatic ESDPT in the 7AI dimer results in a $7AI^{T}$*/$7AI^{T}$ form (Figure 1b) consisting of an excited and an unexcited proton-transfer tautomer (* represents the excited state). Since both host and guest molecules change their structures, the ESDPT is a **noncatalytic** process in which 7AI in the dimeric form acts not as a catalyst but rather as a reactant. The latter case is important from a chemistry perspective. In the acetic acid catalyzed ESDPT reaction, the 7AI* → $7AI^{T}$* tautomerization has been estimated to be ~13 kcal/mol exothermic.[27] Since the noncatalytic type of ESDPT requires simultaneous tautomerization for both 7AI and its guest molecule, this process, from the energy viewpoint, provides ~13 kcal/mol excess energy for the guest molecule to undergo the tautomerization. Therefore, it is plausible that a chemically important isomer of the guest molecule can be produced via the ESDPT process, which cannot be otherwise accessed.

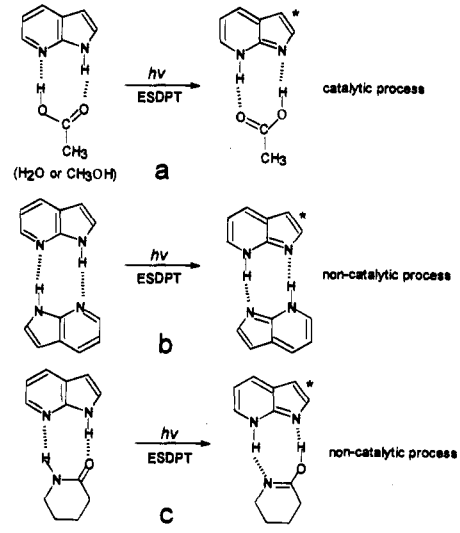
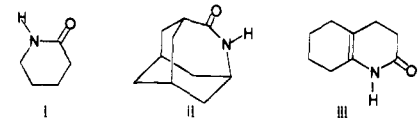


Figure 1. Types of ESDPT reactions: (a) catalytic and (b, c) noncatalytic. While process c can be generalized to various lactams, the lactam **I**/7AI hydrogen-bonded complex is shown.

To test the above concept, the lactam−lactim tautomerization has attracted our attention since the lactam form provides both proton donor (NH) and acceptor (C=O) sites with an optimum geometry. Thus, the formation of a 1:1 lactam/7AI hydrogen-bonded complex, a precursor for the ESDPT reaction, is expected (Figure 1c). In this study 2-azacyclohexanone (**I**), 4-azatricyclo[4.3.1.$1^{3,8}$]undecan-5-one (**II**), and 3,4,5,6,7,8-hexahydro-2(1*H*)-quinolinone (**III**) are selected. Both proton



NMR and IR studies have shown that for **I**−**III** the lactam form is the predominant species in the ground state.[28] The formation of a ground-state lactam/7AI hydrogen-bonded complex is indicated by the significant change of the UV−vis absorption spectra in 7AI containing various concentrations of **I**−**III** in comparison to that of the 7AI monomer (Figure 2). On the basis of the formation of a 1:1 7AI/lactam complex the association constant, K_{ac}, was calculated to be 2.3×10^3 M^{-1} (ϵ_{310} = 1620 cm^{-1} M^{-1}), 2.7×10^3 M^{-1} (ϵ_{310} = 1570 cm^{-1} M^{-1}), and 3.4×10^3 M^{-1} (ϵ_{310} = 1645 cm^{-1} M^{-1}) for **I**/7AI, **II**/7AI, and **III**/7AI complexes, respectively.[29] The room temperature fluorescence spectra (Figure 3 and inset A) show that increasing lactam **I** concentration corresponds to an increase of the 7AI tautomer ($7AI^{T}$*) emission (λ_{max} = 480 nm, τ_f = 2.63 ns) and a decrease of the 7AI normal emission (λ_{max} = 320 nm, τ_f = 1.65 ns). A plot of the inverse of the fluorescence intensity at 500 nm ($1/F_{500nm}$) versus $1/C_M$ (C_M denotes the concentration of the added lactam concentration) gives a straight line (Figure 3B,[30]), indicating that the formation of a 1:1 **I**/7AI complex is the precursor for the observed tautomer emission. According to Figure 3B K_{ac} was calculated to be 2.0×10^3 M^{-1}, consistent with that measured from the absorption spectroscopy. Similar results were also observed for the **II**/

† National Chung Cheng University.
‡ Fu Jen Catholic University.
* Author to whom correspondence should be addressed.

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(26) The ESDPT reaction in Figure 1a is stoichiometric and hence, strictly speaking, is not a catalytic process. However, we simply treat the 7AI proton transfer tautomer as a product. Therefore, acetic acid is defined as a catalyst since its structure remains unchanged during the reaction.
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(28) For example, I shows exclusively a typical secondary amide C=O stretch at 1648 cm^{-1}. This in combination with only one type of amide proton (δ = 6.75 in $CDCl_3$) indicates that the lactam form is the only isomer of I in the solution phase.
(29) The Benesi−Hildebrand equation, $1/A_{310} = [1/(\epsilon_{310}C_0K_{ac})](1/C_M) + [1/(\epsilon_{310}C_0)]$, was used to calculate K_{ac}, where A_{310} denotes the absorbance of the 1:1 lactam/7AI complex at 310 nm. ϵ_{310} is the absorption extinction coefficient of the complex at 310 nm, and C_0 is the initial 7AI concentration.

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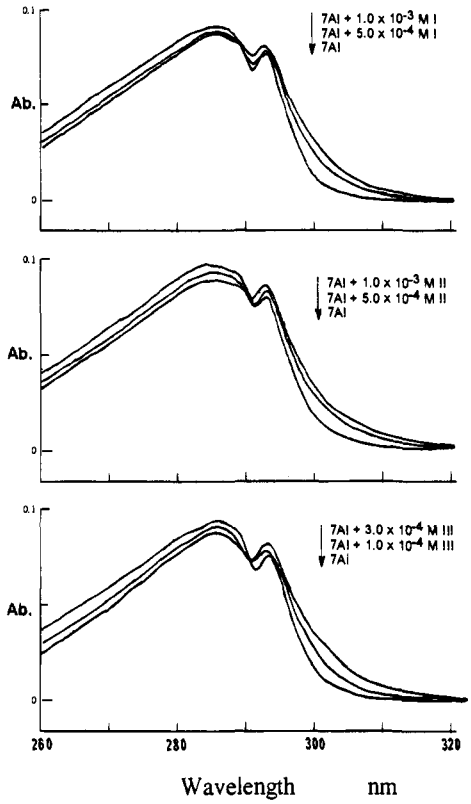

Figure 2. The absorption spectra of 7AI (1.0×10^{-5} M) in cyclohexane with the addition of various concentrations of (a) **I**, (b) **II**, and (c) **III**. Ab. on the y axis denotes the absorbance. In plot c, the background resulting from the absorption of **III** at <300 nm has been subtracted.

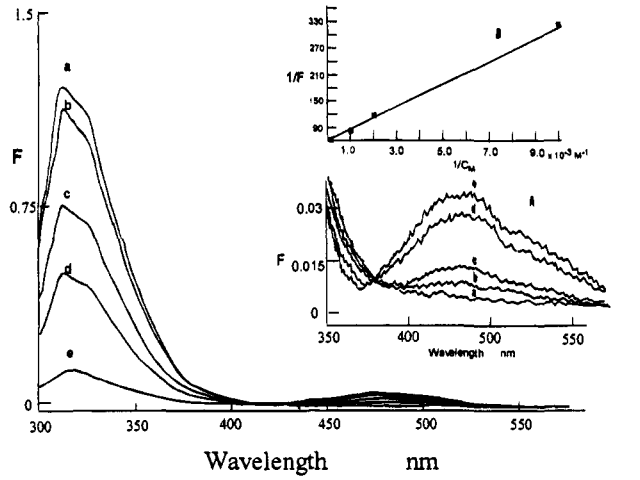

Figure 3. The fluorescence spectra of 7AI (1.0×10^{-5} M) as a function of the concentration of **I** in cyclohexane (λ_{ex} = 290 nm): (a) 0.0 M, (b) 5.0×10^{-5} M, (c) 1.0×10^{-4} M, (d) 5.0×10^{-4} M, (e) 1.0×10^{-3} M. F on the y axis denotes the fluorescence intensity. Insets: (A) the enlarged region, 350–550 nm, of the emission spectra; (B) plot of the inverse of fluorescence intensity ($1/F$, arbitrary unit) at 500 nm versus $1/C_M$. For B the excitation wavelength is 310 nm.

7AI complex (λ_{max} = 320 nm, τ_f = 1.70 ns for 7AI emission and λ_{max} = 480 nm, τ_f = 2.65 ns for $7AI^{T*}$ emission), indicating that the structural flexibility of the amide functional group makes a negligible contribution to the observed ESDPT reaction. The possibility of the tautomer emission resulting from the lactam/7AI exciplex was eliminated through the observation of a lactam concentration-independent, instrument-response-limited (5×10^9 s^{-1}) tautomer fluorescence rise time at 500 ± 10 nm. In conclusion, the nonradiative decay of the excited 1:1 **I** (or **II**)/7AI complex is dominated by the double proton transfer reaction ($k_{pt} > 5.0 \times 10^9$ s^{-1}), resulting in a tautomer emission. *In contrast, although K_{ac} for **III**/7AI measured from the absorption spectroscopy is the greatest among the three 7AI hydrogen-bonded complexes, the tautomer emission at 450–550 nm, under the detection limit, cannot be resolved in any concentration of **III** added to 7AI.* Instead, the intensity of the normal emission decreases, and the spectral feature remains unchanged. A plot of $1/F_{330\ nm}$ versus $1/C_M$ also gives a straight line with K_{ac} of 3.0×10^3 M^{-1}, indicating that the decrease of the normal emission is mainly due to the formation of the **III**/7AI complex in the ground state.

The results may be rationalized by a lactam–lactim tautomerization energy dependent ESDPT reaction. *Ab initio* calculations of the enthalpy of formation for **I**–**III** and their lactim isomers were carried out with 6-31G* as the basis set under full geometry optimization. The results indicate that the endothermicity of lactam → lactim conversion is in the order **III** (13.6 kcal/mol) > **II** (12.1 kcal/mol) ~ **I** (11.9 kcal/mol). Since the tautomerization of each excited 7AI requires a simultaneous lactam–lactim tautomerization of **I**–**III** in the ground electronic level, it is reasonable to predict that the exothermicity of the ESDPT is in the order **I**/7AI* > **II**/7AI* > **III**/7AI* and is energetically unfavorable in the case of the **III**/7AI* complex. For this case, the dynamics of the decay for the **III**/7AI* complex may be exclusively dominated by a non-ESDPT type of radiationless pathway, most likely through a nonradiative channel induced by the dual hydrogen-bonding interaction.[31] However, there are other possible quenching mechanisms. From the dynamic viewpoint, the result may simply indicate the difference in the activation energy barrier of ESDPT among the three complexes, in which a significant barrier may be associated in the ESDPT for the **III**/7AI complex. Therefore, the proton transfer is frustrated during the life span of the **III**/7AI* complex. It is noted that whether the intrinsic excited-state proton transfer has a measurable barrier in a variety of 7AI hydrogen-bonded complexes has been somewhat controversial.[32] Another equally justified hypothesis would be that the reaction does occur in **III**/7AI* but the proton transfer tautomer emission is strongly quenched. The nonradiative rate for the tautomer emission has been found to be much greater than that of the normal form in various 7AI/alcohol hydrogen-bonded complexes.[19] More experimental and theoretical works are needed to resolve this issue.

The spectroscopic evidence of 7AI-assisted lactam–lactim tautomerization through the ESDPT reaction suggests an important photosynthetic pathway. In the catalytic type of 7AI hydrogen-bonded complexes, the ESDPT followed by the $7AI^{T*}$ → $7AI^T$ relaxation produces the guest molecule/$7AI^T$ complex in the ground state, which will undergo a rapid guest molecule catalyzed $7AI^T$ → 7AI reverse proton transfer. On the other hand, the noncatalytic ESDPT may give rise to a stable isomer of the guest molecule (i.e., a product) so that the ground-state reverse proton transfer of this product/$7AI^T$ hydrogen-bonded complex is energetically unfavorable. Consequently, the product is formed, and 7AI can be regenerated through the formation of $7AI^T$ dimer followed by the ground-state reverse proton transfer, establishing a novel photosynthetic pathway triggered by ESDPT.

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(30) Since the absorbance at 310 nm is very small (<0.05), the Benesi–Hildebrand equation can be rewritten as $1/F_{500} = [\alpha/(\epsilon_{310}C_0K_{ac})](1/C_M) + [\alpha/(\epsilon_{310}C_0)]$, where F_{500} is the tautomer relative fluorescence intensity at 500 nm and α is an instrumentation factor.

(31) The decay monitored at 320–360 nm is fitted well by a single-exponential component (τ = 1.62 ns, χ^2 = 1.01) and is ascribed to the 7AI monomer emission. It is believed that the **III**/7AI normal emission is negligibly small and the nonradiative decay rate is greater than our instrument response.

(32) The slow rate of ESDPT measured in alcohol/7AI complexes is generally explained by the rate-limiting solvent reorganization, forming a precursor for the ESDPT. The intrinsic ESDPT on this precursor is believed to be rapid (less than several picoseconds).[9,12,19,21] However, ref 23 has a contradictory conclusion about the intrinsic rate of excited-state proton transfer. In addition, it should be noted that the rate of ESDPT with nanosecond duration has been reported by Fuke and Kaya[11] in the 7AI/1-azacarbazole complex.