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Article

Photo-induced Proton Transfer Promoted by Peripheral Subunits for Some Hantzsch Esters

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ABSTRACT: It is noted that, for a small series of 3,5-diacetyl-1,4-dihydrolutidine (DDL) derivatives and the corresponding Hantzsch esters, the presence of methyl groups at the 2,6-positions serves to extinguish fluorescence in solution but not in the solid state. Emission is weakly activated and affected by changes in solvent polarity. The latter situation arises because the optical transition involves intramolecular charge transfer. Calculations, both semi-empirical and DFT, indicate that, in all cases, rotation of the carbonyl function is facile and that the dihydropyridine ring is planar. These calculations also indicate that the 2,6-methyl groups do not affect the generic structure of the molecule. It is proposed that illumination increases the molecular dipole moment and pushes electron density towards the carbonyl oxygen atom. Proton transfer can now occur from one of the methyl groups, leading to formation of a relatively low-energy, neutral intermediate, followed by a second proton transfer step that forms the enol. Reaction profiles computed for the ground-state species indicate that this route is highly favored relative to hydrogen transfer from the 4-position. The barriers for light-induced proton transfer are greatly reduced relative to the ground-state process but such large-scale structural transformations are hindered in the solid state. A rigid analogue that cannot form an enol is highly emissive in solution, supporting the conclusion that proton transfer is in competition to fluorescence in solution.

KEYWORDS: Hantzsch esters / fluorescence / transition state / hydrogen transfer / keto-enol

INTRODUCTION

Formaldehyde is one of the more harmful air pollutants^{1,2} due to its relatively high atmospheric concentration in urban environments and its deleterious impact on human health. Indeed, it has been classified as carcinogenic by IARC.³ Such concerns mean that there is a need for reliable but straightforward analytical protocols to enable the routine monitoring of formaldehyde vapors; in practical terms, such analyses are most conveniently performed after extraction of gaseous formaldehyde into water.^{1,4-7} In seeking to develop sensitive ways to monitor the presence of formaldehyde in aqueous solution, we were drawn to the *in-situ* formation of fluorescent 3,5-diacetyl-1,4-dihydrolutidine (DDL)

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derivatives.⁸⁻¹⁶ Although this earlier work focused mostly on identification of water-soluble DDL derivatives, it was noted that the fluorescence properties of these compounds were highly sensitive to the nature of substituents in close proximity to the ring nitrogen atom. We set out now to examine the origin of this observation.



Chart I. Generic formulae for the DDL-type derivatives and the corresponding Hantzsch esters described herein.

In so doing we note that these DDL derivatives, being members of the 1,4-dihydropyridine family, are closely related to the so-called Hantzsch esters, which are already known to display solvent-dependent fluorescence spectral properties.¹⁷ Both DDL and Hantzsch esters (Chart I) can be formed by reactions of formaldehyde under rather mild conditions and might be adapted as fluorescent markers for the presence of this analyte in solution.¹⁸ To aid the mechanistic studies, a small series of 1,4-dihydropyridine derivatives has been prepared and fully characterized. Included within this series is a rigid derivative that inhibits internal rotation of the carbonyl functions. It is evident that the Hantzsch esters exhibit the same relationship between fluorescence quantum yield and molecular topology as observed for the DDL derivatives. Specifically, the presence of methyl groups at the 2,6-positions extinguishes emission in solution but not in the solid state. There is no obvious structural reason for this observation.

RESULTS and DISCUSSION

The target compounds are depicted in Chart II and make use of complementary synthetic approaches to prepare the DDL derivatives and the corresponding Hantzsch esters. In particular, a new synthetic

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procedure was devised, starting from propargylic esters, for the synthesis of compounds **1** and **2**. A more conventional procedure was adapted to prepare the 1,4-dihydropyridine derivatives **3-6**. The former method makes use of a condensation reaction involving the propargylic ester with *para*-formaldehyde and ammonium acetate, as is illustrated by way of Scheme 1. It might be noted that this latter reaction, which is performed under mild conditions, has particular relevance for the introduction of an analytical protocol for detection of formaldehyde. The intention is to develop this routine as a means by which to establish viable fluorescence-based tests for the presence of formaldehyde.



Chart II. Chemical formulae and reference numbers for the compounds examined in this contribution.

It should be noted that the pivotal propargylic ester was prepared according to Scheme 2. Here, the tolyl ester **A** requires deprotonation of the acetylenic unit, followed by reaction with ethyl chloroformate. Preparation of the 1,4-dihydropyridine derivatives follows a standard procedure based on condensation of the appropriate acetylacetonate derivative with *para*-formaldehyde and ammonium

acetate, as is outlined by way of Scheme 3. Reaction yields are high and isolation of the final product is

straightforward.



Scheme 1. General synthetic protocol used for preparation of compounds 1 and 2.



Scheme 2. Outline of the methodology employed for the preparation of precursor A.



Scheme 3. Outline of the Hantzsch synthesis adapted to prepare the target compounds, starting from either the acetylacetone derivative or the dimedone substrate.

In the absence of X-ray crystal structural data, quantum chemical calculations (DFT/B3LYP/6-311G**/CPCM) were performed in order to establish lowest-energy conformations for these compounds. The first important feature relates to the conclusion^{19,20} that the six-member ring, in each compound, is in essence planar (Figure 1). This observation, which is in excellent agreement with an earlier X-ray crystallographic study,^{21,22} is consistent with the inclusion of dipolar resonance forms as part of the overall electronic signature of the molecular structure. It might be noted that the presence of aryl groups at the 4-position causes the ring to buckle.^{23,24} Molecular planarity of our compounds is supported by the observation that the C₄-N-H angle is very nearly 180⁰ in each case. Other informative structural outputs include the N-C₂, C-O and C₂-C₃ bond lengths as compiled in Table 1, and the corresponding dihedral angles between the ring and the carbonyl residues.



Figure 1. Energy-minimized structure computed (DFT/B3LYP/6-311G**/CPCM) for **4** (N blue, O red, C gray and H white).

We can begin a discussion of these findings by reference to the DDL-like analogue 4. Here, the lowest-energy conformation has the two carbonyl groups directed towards the lower rim of the planar dihydrolutidine ring (Figure 1); again, this observation is in excellent agreement with a prior crystal structure determination.^{21,22} The dihedral angles between the ring and carbonyl groups are close to 0⁰. However, internal rotation, calculated²⁵ by DFT (B3LYP/cc-pVTZ0) methods, is facile, and the structure with one carbonyl group pointing away from the ring is destabilized by only ca. 1 kJ/mol (Figure 2). This "instability" is caused by slight steric crowding due to the presence of hydrogen atoms ACS Paragon Pfus Environment

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on the proximal methyl groups. The computed structure having both carbonyl groups pointing away from the ring is only marginally (i.e., <4 kJ/mol) less stable. As the corresponding dihedral angle increases, there is a concomitant increase in the molecular dipole moment, calculated²⁶ by DFT (B3LYP/aug-cc-pVTZ) methods, from 2.1D for the lowest-energy conformer to 9.4D with one twisted carbonyl group and 17.8D with two twisted carbonyl units. The ease of rotation means there will be a wide distribution of geometries present at any given moment. The rigid DDL-like compound, **6**, has a large dipole moment of 14.8D since the carbonyl groups are directed away from the dihydropyridine ring (Table 1).



Figure 2. Effect of changing dihedral angle on the total energy (open circles) and molecular dipole moment (filled circles) for rotation of one of the carbonyl functions present in compound **4**.

Identical (DFT/B3LYP/cc-pVTZ0) calculations²⁶ made for the 3,5-diethylester-1,4-dihydropyridine derivatives confirm that the carbonyl groups tend to align with the dihydropyridine ring, having no real preference for pointing towards or away from the ring. The energy barriers for full rotation rotation of the carbonyl groups are modest (e.g., 8.8 kJ/mol for **1** and 8.0 kJ/mol for **3**). The phenyl analogue, **5**, positions the aryl rings at a dihedral angle of ca. 75^{0} with respect to the dihydropyridine ring and there is a small (i.e., 7 kJ/mol) barrier to rotation of the ester unit. Steric crowding between the ethyl group and the phenyl ring limits full rotation of these subunits and the carbonyl groups show a slight preference for

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pointing towards the ring. The closest hydrogen-bonding type interactions are found for the ester O atom and the C1-methyl group in **3**, where the shortest distance is ca. 2.1 Å. For **1**, this closest approach is relaxed slightly to 2.3 Å.

Table 1. Structural data computed (DFT/B3LYP/6-311G**/CPCM) for the various target compoundsembedded in a solvent reservoir of dielectric constant = $78.^{a,b}$

Property	4	1	6	5
N-H / Å	1.027	1.023	1.024	1.027
C_3 -N-H / ⁰	179.9	179.3	179.7	179.7
C_1 -N-H / ⁰	118.8	119.8	119.5	118.6
C_5 -N-H / ⁰	118.8	119.9	119.5	119.0
C=O / Å	1.224	1.225	1.226	1.230
	1.225	1.225	1.227	1.230
$C_1 = C_2 / Å$	1.366	1.361	1.363	1.368
C4=C5 / Å	1.367	1.361	1.364	1.369
$C_1-C_2-C-O / ^0$	6.8	0.00	176.5	0.05
$C_5-C_4-C-O / {}^0$	3.6	1.3	177.5	0.2

^aFor atom labeling see compound **1** in Chart II. ^bUncertainty in bond lengths ± 0.001 Å and in bond angles 0.05° .

The absorption and emission spectra of the target compounds presented in Chart II were recorded in polar solvents, such as propan-2-ol, ethanol, water or mixtures thereof, and an example is given as Figure 3 (see Figures S1 to S5 for other examples). The absorption spectra are comparable along the series and show several unstructured maxima, with the higher-energy band seen at about 270 nm being assigned to the $\pi \rightarrow \pi^*$ transition of the α,β unsaturated ester or ketone.²⁷ In some cases, this transition lies closer to 250 nm. The characteristic featureless absorption band appearing within the 350 to 450 nm range is possibly due to a charge-transfer transition between the NH fragment and the conjugated electron-withdrawing acetyl or ester groups.¹⁷ Bathochromic shifts of 5 and 13 nm are found for this transition, respectively, for compounds **4** and **6** on moving from ethanol to water, but the band-shape

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remains unchanged. Similar shifts were found throughout the series. It might be noted that the apparent ε_{MAX} derived for the DDL derivative 4 decreases from 7,500 M⁻¹ cm⁻¹ in propan-2-ol to 4,200 M⁻¹ cm⁻¹ in water, probably indicating that this compound has limited solubility in water. This is not so for the other compounds but none of the compounds are expected to be highly soluble in water.



Figure 3. Representative example of absorption $(2.0 \times 10^{-4} \text{ M}; \text{ black curve at higher energy}), fluorescence <math>(2.0 \times 10^{-5} \text{ M}; \text{ black curve at lower energy})$ and excitation $(2.0 \times 10^{-6} \text{ M})$ circles) spectra recorded for **1** in propan-2-ol at room temperature.

Compounds 1 and 6 are intensely fluorescent in solution and weakly in the solid state (Table 2). The other compounds exhibit rather weak fluorescence in propan-2-ol solution at room temperature but emission is readily detected in the solid state (see Figures S6 to S11). In each case, the emission spectral profile is fairly broad, lacking in fine structure, and subjected to a considerable Stokes' shift (SS). Indeed, the latter parameters range from 3,700 to 4,500 cm⁻¹ in propan-2-ol when the respective peak maxima, values for λ_{ABS} and λ_{FLU} being given in Table 2, are used. These spectral shifts should be considered as exaggerations of the true situation, however, since both absorption and emission spectra are complex compilations of overlapping bands. Indeed, spectral deconstruction of the absorption profile

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recorded for the various Hantzsch esters in propan-2-ol indicates that the (0,0) transition is located at ca. 25,000 cm⁻¹ while that for **4** is red-shifted to about 23,500 cm⁻¹ (Table 2). The rigid DDL derivative, **6**, gives an intermediate value of 24,660 cm⁻¹. The most satisfactory spectral deconstruction indicates that a medium-frequency stretching vibration of 1,450 and 1,610 cm⁻¹, respectively, accompanies the absorption process for the esters and DDL-like compounds. A representative example of this spectral deconstruction is given as part of the Supporting Information (Figures S12-S17).

 Table 2. Summary of spectroscopic properties recorded for the target compounds at room temperature.

Cmpd	$\lambda_{ABS}^{a}(nm)$	$\lambda_{FLU}^{\ \ b}$	ε _{MAX} c	SS ^d	λ_{FLU}^{e}	$\Phi_{ m FLU}{}^{ m f}$	$\Phi_{\mathrm{FLU}}{}^{\mathrm{g}}$	$\tau_{\rm S}{}^{\rm f}$
		(nm)	$(M^{-1}.cm^{-1})$	(cm^{-1})	(nm)			(ns)
1	378 ^h	456	8600	1900	461	0.47	0.02	7.3
	367 ⁱ	436	5200			0.51		6.3
	378 ^j	433	1600			0.37		
	368 ^k	437	3800			0.50		
2	373 ^h	488	5600	2350	500	< 0.001	0.08	<1
3	375 ^h	455	8200	2150	460	0.02	0.18	<1
	357 ⁱ	445	6400			0.006		<1
	375 ^j	458	6900			0.017		<1
	356 ^k	437	6200			0.008		<1
4	408 ^h	494	7500	2560	482	0.02	0.08	<1
	392 ⁱ	486	5050			0.007		<1
	404 ^j	488	5100			0.023		<1
	391 ^k	479	4400			0.007		<1
5	374 ^h	461	3700	2280	474	< 0.001	0.17	<1
	366 ⁱ	415	2050			< 0.001		<1
	375 ^j	481	2300			< 0.001		<1
	365 ^k	470	2600			< 0.001		<1
6	389 ^h	447	9100	2020	448	0.59	0.02	7.8
	374 ⁱ	427	6100			0.74		9.1
	385 ^j	442	6300			0.48		
	368 ^k	435	3900		<u> </u>	0.20		

^aMaximum of the lowest-energy absorption band recorded in solution. ^bMaximum of the fluorescence peak recorded in solution. ^cEffective molar absorption coefficient measured in a certain solvent. ^dStokes' shift calculated for deconstructed absorption and emission spectra recorded in propan-2-ol. ^eMaximum of the fluorescence peak recorded in a compressed KBr disk. ^fFluorescence quantum yield or excited-state lifetime determined in a certain solvent. ^gFluorescence quantum yield determined in a KBr disk. ^hPropan-2-ol. ⁱDichloromethane. ^jDimethylsulfoxide. ^kToluene.

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Absorption spectral data collected for the phenyl derivative, **5**, and the rigid DDL compound, **6**, show somewhat anomalous ε_{MAX} values (Table 2) for the lowest-energy absorption transition. The former derivative has a lower than expected ε_{MAX} while the latter has a somewhat higher value, although the spectral profiles and peak energies are not dissimilar to those recorded for the other species. Close examination of absorption spectra recorded for **5** shows the presence of a low-energy tail that corresponds to what might be anticipated for light scattering caused by the presence of particulate matter.²⁸ We conclude, therefore, that this derivative is poorly soluble in alcoholic solvents.



Figure 4. Kohn-Sham representations of the HOMO (upper panel) and LUMO (lower panel) computed (DFT/B3LYP/6-311G**/water reservoir) for compound **3** at an iso-density of 0.015.

Molecular orbital calculations²⁹ carried out with the energy-minimized structures are fully consistent with the lowest-energy absorption transition having partial charge-transfer character. Thus, the HOMO is localized on the dihydropyridine ring and includes a marked contribution from the N atom. In contrast, the LUMO is spread over much of dihydropyridine ring, but not the N atom, and includes the

carbonyl groups (Figure 4). Excitation, therefore, will transfer electronic charge from the N atom to the carbonyl group. The optimized ground state structures computed in water using the conductor-like polarizable continuum model³⁰ were used for single-point TD-DFT (CAM-B3LYP) calculations³¹ to predict the excited-state dipole moments and excitation energies, recognizing that there are problems for such calculations for molecules with substantial charge-transfer character.³² Indications are that there is an increase in the molecular dipole moment of about 2D, in each case. This appears to be a small change but, because the conjugation lengths are short, excitation is likely to lead to a substantial increase in the contribution of the dipolar resonance forms. Compound 6 has the highest ground state dipole moment ($\mu_{GS} = 14.8D$), but a small increase ($\Delta \mu = 1.7D$) upon excitation, which might contribute towards the somewhat enhanced ε_{MAX} value. In all cases, the computed excitation energies were underestimated compared to the experimental values by ca. 10%. The calculated and observed transition energies could be brought into closer alignment by varying the hybrid functional, as has been demonstrated for a range of charge-transfer compounds.³² None of these calculations indicate the likely presence of close-lying excited states. The amount of charge-transfer character associated with the ground-state molecules, based on the orbital composition analysis,³³ ranges from 0.32 to 0.65 for compounds 4 and 6, respectively.

As mentioned above, these compounds fluoresce to varying degrees, both in propan-2-ol at room temperature and after dispersion in a KBr pellet. The emission spectra recorded in dilute solution can be deconstructed into accompanying vibronic bands, as was done for the corresponding absorption spectra. The resulting vibrational envelopes can be assigned to medium-frequency stretching modes of 1,400 cm⁻¹ for the Hantzsch esters and 1,600 cm⁻¹ for the DDL-like compound. The spectrally resolved data allow derivation of corrected Stokes' shifts (Table 2). Now, it appears that the Hantzsch esters exhibit Stokes' shifts of ca. 2,000 cm⁻¹ while the DDL-like derivative **4** shows a more substantial shift of 2,600 cm⁻¹. The rigid DDL-like compound **6** has a less pronounced Stokes' shift (SS = 2,020 cm⁻¹) than its more flexible counterpart. This situation seems reasonable since **6**, which is the most polar of the compounds, is less susceptible to large-scale geometry changes on excitation. For **4** and **6**, the **ACS Paragon Plas Environment**

fluorescence maxima are red shifted by 18 and 11 nm, respectively, in water relative to propan-2-ol, an observation that is fully consistent with the proposed intramolecular charge-transfer character.³³

The fluorescence quantum yields (Φ_{FLU}) measured in propan-2-ol range from 0.02 to 0.59 (Table 2). This level of variation, taken in conjunction with the minor structural changes, is surprising but in keeping with previous measurements⁸⁻¹⁶ made for DDL-like derivatives. In generic terms, it appears that substitution at the 2,6 position of the dihydropyridine ring results in a major loss of fluorescence in solution. However, the rigid derivative, **6**, is the most intensely fluorescent compound. In each case, there is excellent agreement between absorption and excitation spectra. For the strongly emissive compounds, the excited-state lifetimes (τ_S) are around 7 ns (Table 2) and allow estimation of the corresponding radiative rate constants (k_{RAD}) as being ca. 6.5 x 10⁷ s⁻¹ in solution.



Figure 5. Temperature dependence recorded for compound 4 in a mixture of C_2H_5OH and H_2O (1:9), the arrow indicating the direction of increasing temperature. The insert shows Arrhenius-type plots for a mixture of ethanol and water (1:9) (filled gray circles), water (open circles) and propanol-2-ol (filled black circles).

Table 3. Parameters derived from an Arrhenius-style analysis of the temperature effect on the fluorescence recorded for the various dyes in solution.

Compound	Propan-2-ol	Water	Water/ethanol 9/1
	$E_A{}^a$: A^b	$E_A{}^a$: A^b	$E_A{}^a$: A^b
1	6.8 : 1.4	NA	NA
3	18.0 : 2500	NA	NA
4	18.0 : 1900	5.9 : 50	7.6 : 90
6	3.8:0.25	NA	0.7:0.09

^aActivation energy in units of kJ/mol. ^bPre-exponential factor in units of 10⁹ s⁻¹.

For the two DDL-like compounds, **4** and **6**, temperature dependent emission studies were carried out in both propan-2-ol and a 9/1 mixture of water/ethanol (Figure 5 and see also Figures S18-S21). Although the experimental data are highly restricted, it appears that both compounds display weakly activated emission in solution. On fitting the data to an Arrhenius-style model, it turns out that in water/ethanol 9/1 the activation energies for **4** and **6**, respectively, are 7.6 and 0.7 kJ/mol. Somewhat higher barriers are found in propan-2-ol, individual values being 18.0 and 3.8 kJ/mol respectively for **4** and **6**, whereas a smaller barrier of only 5.9 kJ/mol is found for **4** in water. The pre-exponential factors follow the same trend (Table 3), decreasing as the solvent polarity increases and being markedly higher for **4** relative to **6**. In propan-2-ol, activation barriers of 6.8 and 18.0 kJ/mol, respectively, were determined for **1** and **3**, again with quite disparate pre-exponential factors (Table 3). The more fluorescent compounds, namely **1** and **6**, possess the smaller activation barriers and, more importantly, the significantly lower pre-exponential factors.

Our understanding of the spectroscopic properties of these compounds can now be summarized as follows: Each of the compounds is bipolar; a conclusion reached from the quantum chemical calculations and supported by their solubility characteristics. Excitation leads to an increased dipole moment, as evidenced by the pronounced Stokes' shifts, solvent dependence and calculations. The barriers for rotation of the carbonyl groups are very small, except for **6**. The temperature dependence studies indicate the existence of a dark species that is strongly coupled to the ground state and easily

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reached from the fluorescent state, except for **1** and **6**. Compounds having methyl groups at the 2,6positions of the dihydropyridine ring undergo more rapid nonradiative deactivation than either nonsubstituted Hantzsch esters or the rigid derivative **6**. According to the structural calculations, the methyl group does not prevent the carbonyl group from aligning with the dihydropyridine ring.

In attempting to rationalize these findings it is tempting to invoke formation of an enol³⁴ whereby the hydrogen attached at the pyridine N atom is transferred to one of the carbonyl oxygen atoms (Chart III). At the concentrations used throughout this work, bimolecular reactions are most unlikely and, in any case, emission is restored in the solid state where there is more likelihood for close associations. Enol formation might be promoted by specific interactions with solvent molecules but this does not explain the importance of the methyl groups. Instead, we have considered the possibility of intramolecular proton transfer.



Chart III. Proposed chemical formulae for the keto/enol equilibrium available for compound **1**, with the dipolar keto species playing a key role in long-range proton transfer.

For **1**, enolisation would require an unacceptably long-range proton-tunneling step, unless hydrogen transfer from the C3-position of the dihydropyridine ring to the carbonyl oxygen atom plays an intermediary role. With compound **4**, it might be that enolisation is promoted by proton transfer from the methyl group (Scheme 4). Calculations^{34,35} (DFT/B2LYP/6-311G**/CPCM) indicate that the enol

derived from **4** is less stable than the keto form by some 72 kJ/mol in water at the ground-state level. Identical calculations made for the various 1,4-dihydropyridine derivatives indicate that the enol is less favorable than the keto form by 101, 107 and 173 kJ/mol, respectively, for **1**, **3** and **6**. As such, enolisation is unlikely to take place in the dark. This situation is in good agreement with the structural characterization studies that clearly indicate the exclusive presence of the keto form. It might be noted in passing that the enols derived from **1**, **3** and **6** are planar but, because of steric clashes between proximal methyl hydrogen atoms, that derived from **4** is slightly distorted around the dihydropyridine unit (Figure **6**).



Scheme 4. Proposed scheme for enol formation for compound 3 illustrating the role played by the 2methyl group in proton transfer.

Recognizing the thermodynamic difficulties for enolisation in the ground state, an intrinsic reaction profile was computed for 4 at the DFT (B3LYP/6-311G**/CPCM) level (Figure 7). Mutual rotation of the carbonyl and methyl groups is facile while proton transfer from the C1-methyl group to the proximal carbonyl oxygen atom (O····H separation is ca. 1.95 Å) gives rise to a relatively low energy intermediate (species A in Figure 7). A well-defined transition state (TS1 in Figure 7) can be identified for this reaction and the computed barrier for the ground-state reaction is 103 kJ/mol. For TS1, the relevant

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O···H bond length is 1.203 Å but the overall geometry around the ring is far from planar (Figure 7). Species A can react further to form the enol. Now, a substantial barrier of 310 kJ/mol is involved in forming the respective transition state (TS2 in Figure 7). This latter species has a highly distorted geometry (Figure 7) with C···H and N···H bond lengths, respectively, of 1.519 and 1.312 Å. Although reaction to form species A seems plausible, it is considered unlikely that formation of the final enol (Scheme 4) will be effective because of the high barrier, unless species A is formed in an excited state. A similar intrinsic reaction profile is found for compound **3** but the rigid analogue **6** cannot react along this coordinate. Likewise, compound **1** cannot reach a suitable transition state because the C₂ hydrogen atom is too distant from the carbonyl oxygen atom. The alternative route of utilizing one of the hydrogen atoms at C₄ involves a high-energy barrier ($\Delta E = 240$ kJ/mol) to reach a dipolar transition state.



Figure 6. Energy-minimized structures computed for the enols derived from compounds 1 (upper panel) and 4 (lower panel).

It will not have escaped attention that those derivatives able to form species A (i.e., 3 and 4 but not 1 or 6) are the compounds that do not fluoresce in solution. In fact, proton transfer from the C₁-methyl ACS Paragon Plus Environment

group to the proximal carbonyl oxygen atom is likely to become more favorable under illumination. This is because of the increased potential energy available to the excited-singlet state, relative to the ground state, and the elevated dipole moment that serves to lengthen the C-O bond and raise electron density on the oxygen atom. The temperature-dependent fluorescence studies indicate substantially lower activation energies for the excited state and attempts to confirm this situation were made by computational approaches.



Figure 7. Intrinsic reaction pathway computed (DFT/B3LYP/6-311G**/CPCM) for the ground state of compound **4**, with the relative electronic energies listed in units of kJ/mol. The embedded structures are calculated geometries for the two transition states; N.B. structures for the keto and enol forms are given in Figures 1 and 6, respectively, while that for species "A" is given in the ESI.

Starting from the optimized (TD-DFT/B3LYP/6-311G**/CPCM) geometry for the excited-singlet state of **4**, an intrinsic reaction coordinate analysis was performed for the conversion to species A. In contrast to the ground state, the barrier for reaching the TS is reduced from 102.8 kJ/mol to only 17.0 kJ/mol. The same analysis performed for **3** gave a reduced barrier of 20 kJ/mol for the excited-singlet state. Although higher than the experimental values, the computed barriers indicate that excited-state proton transfer is easier than for the corresponding ground-state species. A similar conclusion has been reached for prototropic keto-enol tautomerism of certain boron dipyrromethene dyes.³⁵ As such, ACS Paragon Ptus Environment

formation of species A is expected to compete favorably with fluorescence for both **3** and **4**. Such reaction will form species A as a vibrationally hot ground state and therefore the barrier to formation of the final enol remains very high. The most likely fate for species A is a return to the ground state of the keto form, for which the activation barriers are 35 and 20 kJ/mol respectively for **3** and **4**. These structural changes are inhibited in the solid state where the molecules are able to fluoresce under illumination. Proton transfer will not compete with fluorescence for compounds **1** and **6**.

CONCLUDING REMARKS

With the aid of quantum chemical calculations, it has been possible to rationalize the intriguing photophysical properties of some DDL-like derivatives⁸⁻¹⁶ and their corresponding Hantzsch esters. The key supposition involves proton transfer from a proximal methyl group to the carbonyl oxygen atom. This process is facilitated by easy rotation of the carbonyl group that brings the reacting units into reasonably close proximity. Although tempting to invoke enol formation via a second proton transfer step, this additional reaction is not needed to explain the fluorescence yields. The first proton transfer step is fast and favored by internal charge transfer that raises electron density on the carbonyl oxygen atom. The reaction is inhibited in the solid state but further promoted in more polar solvents.

It is interesting to compare the computed structures of the stable species and their respective transition states. With specific reference to **4**, we note that the keto N-H bond and the corresponding enol O-H bond have lengths of 1.007 and 0.962 Å respectively; N.B. the reproducibility of these various bond lengths is on the order of ± 0.001 Å. These values are typical for such species³⁶ and are very similar to those calculated for the Hantzsch esters. The key intermediate, species A, has N-H and O-H bond lengths, respectively, of 1.008 and 0.962 Å. The ring is non-planar and the two C₄ hydrogen atoms reside in quite disparate environments. For TS1, the N-H bond retains a comparable length (i.e., 1.009 Å) to that of the keto form but important structural changes are evident elsewhere. In particular, the O…H length is relatively long at 1.203 Å while the C…H bond is 1.420 Å. The ring is buckled and the C₄ hydrogen atoms are clearly non-equivalent. Moving to TS2, we note that the O-H bond takes on the

characteristic features of a stable structure, the bond length being 0.963 Å. The N···H and C···H bond lengths are 1.312 and 1.519 Å, respectively. These long bonds must make substantial contributions to the energy barrier.

The ability of the C₁-methyl group to promote nonradiative decay of the excited-singlet state is both unusual and unexpected. In biological processes, there is evidence to support the idea of proton transfer between remote sites³⁷⁻⁴⁰ but the mechanism is not at all clear⁴¹ and the role of the solvent has not been fully explored. In certain photo-induced keto-enol tautomerizations (e.g., with 7-hydroxyquinoline⁴²) where the donor and acceptor are too far apart for proton tunneling to be effective it is believed that the reaction is promoted by hydrogen-bonding solvents.^{43,44} Here we provide new insight into how long-range proton transfer might be effected by proximal alkyl groups. A more detailed quantum chemical study should provide deeper insight into the subtleties of this mechanism.

It might be recalled that our initial interest in these molecular systems derives from the need to develop sensitive analytical tests for the detection of formaldehyde present in aqueous solution. In this respect, we have found that fluorescent analogues can be formed under mild conditions provided the C_1 and C_5 sites are without alkyl substituents. Future work will build on this realization and seek to introduce suitable analytical tests using water-soluble analogues. It is also important¹⁷ to identify strategies leading to dyes possessing increased levels of photostability.

EXPERIMENTAL SECTION

General methods: All reactions were performed under a dry atmosphere of argon. All raw chemicals were used as received from commercial sources without further purification. Reaction solvents were distilled according to standard procedures. Thin layer chromatography (TLC) was performed on silica gel or aluminium oxide plates coated with fluorescent indicator. Chromatographic purifications were conducted using (40-63 μ m) silica gel. All mixtures of solvents are given as the v/v ratio. ¹H NMR (400.1 MHz) and ¹³C NMR (100.5 MHz) spectra were recorded at room temperature (rt) on a Bruker Advance 400 MHz spectrometer, ¹H NMR (300.1 MHz) and ¹³C NMR (75.5 MHz) spectra were

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recorded at rt on a Bruker Advance 300 MHz spectrometer, ¹H NMR (200.1 MHz) and ¹³C NMR (50.5 MHz) spectra were recorded at rt on a Bruker Advance 200 MHz spectrometer using perdeuterated solvents as internal standards. The ¹¹B (128 MHz) NMR spectra were recorded at rt with borosilicate glass as reference. FT-IR spectra were recorded using a spectrometer equipped with an ATR "diamond" apparatus. Absorption spectra were recorded using a dual-beam grating spectrophotometer with a Shimadzu UV-3600 spectrophotometer. All fluorescence spectra were recorded with a fully corrected Horiba Fluoromax-4 spectrofluorimeter. The fluorescence quantum yields were determined for optically dilute solutions, having an absorbance less than 0.08 at the excitation wavelength, by comparison to standard compounds. Quinine sulfate⁴⁵ was used as reference (Φ = 0.55 in 1N H₂SO₄, λ_{ex} = 366 nm) for dyes emitting below 480 nm and Rhodamine $6G^{45}$ (Φ = 0.88 in ethanol, λ_{ex} = 488 nm) was used for the other dyes. Luminescence lifetimes were measured on a spectrofluorimeter equipped with an R928 photomultiplier and pulsed laser diode connected to a GwInstect delay generator. The excitation source was a laser diode ($\lambda = 310$ nm). The instrument response function was determined by using a lightscattering solution of LUDOX in water. Solid-state fluorescence and excitation spectra were recorded in KBr pellets of the desired compound dispersed at 10⁻⁶-10⁻⁷ M concentration for emission and excitation spectra measurements using an F-3029 integrating sphere.

Reagents: Ammonium acetate, acetylacetone, dimedone, ethyl acetoacetone, ethyl benzoylacetate, ethyl chloroformate, ethyl propiolate, 4-ethynyltoluene, para-formaldehyde, propane sultone and propiolic acid were purchased from commercial sources. The preparations of compounds 1,⁴⁶ ethyl 3-tolylpropiolate,⁴⁷ 2,⁴⁸ 3,⁴⁹ 4,⁵⁰ and 6⁵¹ were based by the cited references.

Synthesis of 1: To a stirred solution of ethyl propiolate (0.30 mL, 3.10 mmol) in a mixture of ethanol/H₂O solution (5 mL, 1:1) were added *para*-formaldehyde (120 mg, 3.98 mmol) and ammonium acetate (307 mg, 3.98 mmol). The resulting solution was heated at 90°C for 1h. After cooling the solution at room temperature, the reaction mixture was extracted with CH_2Cl_2 . The organic layer was washed twice with water, dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with a mixture of CH_2Cl_2 /ethyl

acetate (95:5) to afford compound 1 as a yellow powder. The solid was recrystallized from $CH_2Cl_2/cyclohexane$ and washed with cyclohexane and pentane. Finally, it was dried under vacuum (120 mg, 17%). ¹H NMR (200 MHz, CDCl₃) δ (ppm): 7.08 (2H, d, J = 4.9 Hz, CH), 5.78 (1H, s, NH), 4.18 (4H, q, J = 7.3 Hz, CH₂CH₃), 3.25 (2H, s, CH₂), 1.27 (6H, t, J = 7.3 Hz, CH₃CH₂).

Synthesis of ethyl 3-tolylpropiolate: To a stirred solution of p-tolylacetylene (0.65 mL, 5.12 mmol) in freshly distilled THF (5 mL) at -78°C was added drop-wise 1.6M n-BuLi in pentane (2.88 mL, 4.61 mmol). The solution was maintained at room temperature during 1h before being returned to -78°C. Ethyl chloroformate (0.49 mL, 5.12 mmol) was added drop-wise. The resulting solution was stirred for 8h at room temperature before being extracted with CH₂Cl₂. The organic layer was washed twice with water, dried with MgSO4 and concentrated under reduced pressure. The crude material was purified by column chromatography on silica-gel, eluting with a mixture of AcOEt/petroleum ether (10:90) to give the desired compound as a yellow oil which was dried under reduced pressure (940 mg, 97%). 1H NMR (200MHz, CDCl₃) δ (ppm): 7.48 (2H, d, J = 8.0 Hz, CH arom), 7.18 (2H, d, J = 8.0 Hz, CH arom), 4.29 (2H, q, J = 6.9 Hz, CH₂CH₃), 2.38 (3H, s, CH₃), 1.35 (3H, t, J = 6.9 Hz, CH₃CH₂).

Synthesis of 2: To a stirred solution of ethyl 3-tolylpropiolate (200 mg, 1.06 mmol) in ethanol (2 mL) were added *para*-formaldehyde (42 mg, 1.38 mmol) and ammonium acetate (106 mg, 1.38 mmol). The resulting solution was heated at 85°C for 5 days. After cooling to room temperature, the reaction mixture was extracted with AcOEt. The organic layer was washed twice with water, dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with a mixture of AcOEt/petroleum ether (70:30) to afford compound 2 as a yellow powder. The solid was recrystallized from AcOEt/pentane and washed with pentane. Finally, it was dried under vacuum (70 mg, 12%). ¹H NMR (300 MHz, CDCl₃) δ (ppm): 7.16 (8H, dd, 3J = 12.0 Hz, 4J = 3.6 Hz, CH arom), 5.45 (1H, s, NH), 3.95 (4H, q, J = 7.2 Hz, CH₂CH₃), 3.58 (2H, s, CH₂), 2.33 (6H, s, CH₃), 0.98 (6H, t, J = 7.2 Hz, CH₃CH₂). 13C NMR (75 MHz, CDCl₃) δ (ppm): 167.44, 146.94, 139.14, 134.04, 129.11, 127.90, 99.96, 59.83, 34.27, 26.01, 22.48, 21.48, 14.20, 14.09, ESI-MS 405.1 (100,

[M]) Elemental analysis for C₂₅H₂₇O₄: Calc: C, 74.05; H, 6.71; N, 3.45. Found: C, 73.88; H, 6.49; N, 3.17.

Synthesis of 3: To a stirred solution of ethyl acetoacetate (9.7 mL, 77 mmol) in ethanol (100 mL) was added *para*-formaldehyde (1.15 g, 38 mmol) and ammonium acetate (4.45g, 58 mmol). The resulting solution was heated at 80°C for 15 min. A pale yellow precipitate formed after cooling to room temperature. The mixture was diluted with water and the yellow suspension was isolated by filtration, washed firstly with water and then with cold ethanol. A recrystallization of the filtrate was made from hot ethanol and the solution was allowed to cool at 0°C. The bright yellow precipitate was removed by filtration, washed with cold ethanol and dried under vacuum (15.4 g, 79%). ¹H NMR (200MHz, CDCl₃) δ (ppm): 5.18 (1H, s, NH), 4.16 (4H, q, J = 7.3 Hz, CH₂CH₃), 3.26 (2H, s, CH₂), 2.18 (6H, s, CH₃), 1.28 (6H, t, J = 6.9 Hz, CH₃CH₂).

Synthesis of 4: To a stirred solution of acetylacetone (10.3 mL, 100 mmol) in ethanol (100 mL) was added *para*-formaldehyde (1.50 g, 50 mmol) and ammonium acetate (3.50g, 50 mmol). The resulting solution was heated at 45°C for 1h. After cooling, a pale yellow precipitate formed. This was isolated by filtration and washed with water. The resulting pale yellow powder was recrystallized twice from hot ethanol. Finally, it was dried under vacuum (16.7g, 86%). ¹H NMR (400MHz, CDCl₃) δ (ppm): 5.42 (1H, s, NH), 3.42 (2H, s, CH₂), 2.22 (6H, s, CH₃CO), 2.17 (6H, s, CH₃).

Synthesis of 5: To a stirred solution of 3-phenyl-1-ethyl acetoacetate (0.27 mL, 1.56 mmol) in a mixture of ethanol/H₂O solution (5 mL, 1:1) were added *para*-formaldehyde (61 mg, 2.03 mmol) and ammonium acetate (157 mg, 2.03 mmol). The resulting solution was heated at 90°C for 1h. After cooling to room temperature, the reaction mixture was extracted with CH_2Cl_2 . The organic layer was washed twice with water, dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with a mixture of AcOEt/petroleum ether (70:30) to give compound 5 as a yellow powder. The solid was recrystallized from AcOEt/pentane and washed with pentane before being dried under vacuum (70 mg, 12%). ¹H

NMR (200MHz, CDCl₃) δ (ppm): 7.35 (10H, m, CH arom), 5.47 (1H, s, NH), 4.20 (4H, q, J = 7.0 Hz, CH₂CH₃), 3.53 (2H, s, CH₂), 0.96 (6H, t, J = 7.3 Hz, CH₃CH₂).

Synthesis of 6: To a stirred solution of dimedone (200 mg, 1.43 mmol) in a mixture of ethanol/H₂O solution (5 mL, 1:1) were added *para*-formaldehyde (56 mg, 0.71 mmol) and ammonium acetate (21 mg, 0.71 mmol). The resulting solution was heated at 90°C for 4h. After cooling to room temperature, a yellow precipitate formed, which was isolated by filtration, washed successively with cold ethanol, diethyl ether and pentane. It was dried under vacuum (120 mg, 36%). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 5.16 (1H, s, NH), 3.12 (2H, s, CH₂), 2.27 (4H, s, CH₂CO), 2.19 (4H, s, CH2), 1.09 (12H, s, CH₃).

Computational methods: A wide variety of quantum chemical calculations were performed based on prior work which concluded that semi-empirical AMI SCF approaches could give satisfactory estimates of the barrier heights for proton transfer in substituted salicylaldehyde anils.³⁶ Semi-empirical methods, using PM6⁵²-RHF(CI)-COSMO⁵³ as implemented by AMPAC.⁵⁴ were used to obtain first estimates for the lowest-energy conformations at both ground- and excited-state levels. Convergence was judged in terms of the steepest descent and conjugate gradients methods. Calculation of second derivatives was made by the Newton-Raphson method. Subsequent refinement of the geometries was made using DFT calculations, by way of Gaussian-09.55 The hybrid Becke-3-Lee-Yang-Parr56-59 (B3LYP) exchange correlation functional was applied. Geometries were fully optimised at the B3LYP level using the 6-311G** basis set. The absence of imaginary frequencies was confirmed for all original structures. Dipole moments were taken from the latter outputs. The same procedure was used to determine geometries and single-point energy levels for the corresponding enols and for intermediates akin to Species A. Related studies, starting with AMPAC and moving to Gaussian-09, addressed the corresponding dipolar intermediates associated with proton transfer from the C4 position to an adjacent carbonyl oxygen atom. In all cases, the solute was embedded in a reservoir of water molecules. The DFT/B3LYP/6-311G** optimised structures were used for subsequent electronic-structure analysis of the HOMO/LUMO iso-surfaces.

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Rotation of the carbonyl function was carried out using semi-empirical methods (PM6-RHF-COSMO) used with the computed geometry for the ground state in a water bath. The relevant dihedral angle was varied systematically, the energy minimised, and a single-point calculation performed using AMPAC. A limited number of molecular dynamics simulation runs were performed using YASARA in order to verify the free rotation of these carbonyl groups.

Transition states were searched within Gaussian-09 using the TS keyword. All transition states were verified by the existence of a single imaginary frequency mode. In all cases, intrinsic reaction coordinate (IRC) calculations were performed to confirm that the transition state connects keto and species A and enol and species A. Activation barriers were taken as the difference between the zero point vibrational energy corrected electron energies for transition state and the stable conformation. These IRC calculations worked well for **1** and **4** but were somewhat less successful for **3**. In contrast, all three compounds could be handled well within AMPAC, although the derived barriers were roughly 15-20 kJ/mol higher than those found by DFT. For compound **3**, related IRC calculations were made with GAMESS.^{60,61} A set of 30 points along a Linear Least Motion (LLM) path connecting the keto and species A was calculated and single point energies at the B3LYP/6-311G** level were calculated again at the B3LYP/6-311G** level.

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SUPPORTING INFORMATION: Provided are absorption, emission and excitation spectra in solution and in the solid state for all compounds. This material is available free of charge via the internet at http://pubs.acs.org.

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SYNOPSIS TOC: A baffling disparity in the fluorescence yield found for a series of 1,4dihydropyridines in solution is nicely explained in terms of an unusually long-range proton transfer involving an intermediary methyl group.

