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Intramolecular Electron Transfer in the Photochemistry of Some Nitrophenyldihydropyridines

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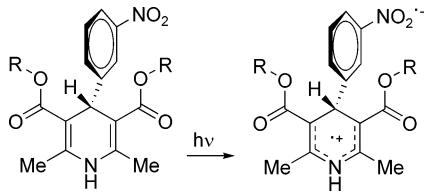

4-Phenyl-1,4-dihydropyridine-3,5-dicarboxylates contain two π chromophores separated by an sp^3 carbon. The lowest singlet is localized on the dihydropyridine moiety ($^1PyH_2$-Ph) and emits a blue fluorescence (with close to unitary efficiency in glass at 77 K). In 3-nitrophenyl derivatives (PyH_2-$PhNO_2$, some of which are photolabile drugs) the fluorescence is completely quenched. Reasonably, this is due to intramolecular electron transfer between the close-lying donor and acceptor moieties to give the charge-separated species ($PyH_2^{\bullet+}-PhNO_2^{\bullet-}$). In EPA glass at 77 K, back-electron transfer gives the dihydropyridine-localized triplet ($^3PyH_2-PhNO_2$), which emits a yellow phosphorescence. In solution, deprotonation from the radical cation on the dihydropyridine moiety initiates rearomatization, finally giving Py-$PhNO_2$ with low quantum yield (5×10^{-4} to 5×10^{-3}, increasing up to 0.013 by irradiation at 254 nm, where direct excitation of the nitrophenyl chromophore contributes). In the presence of triethylamine, the reaction changes to neat reduction of the nitro group. When a tethered alkylamino group is present, oxidative degradation of that moiety occurs, again via an electron-transfer intramolecular process. This has been found with the drug nicardipine, where photodegration is more efficient (Φ 0.02 to 0.1). Donor−acceptor dyads of this type, easily available through the Hantzsch synthesis, may be useful for building new photoinduced electron-transfer systems.

Dihydropyridines are excellent antioxidants.[1] The easily prepared Hantzsch esters (2,6-dialkyl-3,5-dialkoxycarbonyl-1,4-dihydropyridines)[2] have been used in this role for a variety of applications, from modeling NADH in biochemistry[3] to anti-knocking agent in fuels[4] or to photosensitive polymers.[5] Many of these Hantzsch dihydropyridines bear a (substituted) phenyl group in position 4 and thus contain two independent π-systems separate by an sp^3 carbon. The flanking ester groups in positions 3 and 5 are expected to keep the phenyl group roughly perpendicular to the dienaminoester moiety of the dihydropyridine ring, as verified in the crystal structure.[6] Noteworthy, the same, or closely related, molecules are also used in therapy against cardiac diseases for their activity as calcium channel blockers[7a,b] as well as, more recently, for treating pathologies

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(1) Lavilla, R. *Curr. Org. Chem.* **2004**, *8*, 715. Guengerich, F. P.; Okazaki, O.; Seto, Y.; MacDonald, T. L. *Xenobiotica* **1995**, *25*, 689.

(2) Hantzsch, A. *Liebigs Ann.* **1882**, *215*, 1, 72. Watanabe, Y.; Shiota, K.; Hoshiko, T.; Ozaki, S. *Synthesis* **1983**, 761. Kellog, R. M.; van Doren, H.; Hedstrand, D.; Kooi, J.; Kruizinga, W. H.; Troostwijk, C. B. *J. Org. Chem.* **1980**, *45*, 2854. Vanden Eynde, J. J.; Mayence, A. *Molecules* **2003**, *8*, 381. Lavilla, R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1141.

(3) Fukuzumi, S.; Koumitsu, S.; Hironaka, K.; Tanaka, T. *J. Am. Chem. Soc.* **1987**, *109*, 305.

(4) Wang, L. F.; Zhang, H. Y.; Kong, L.; Chen, Z. W.; Shin, J. G. *Helv. Chim. Acta* **2004**, *87*, 1515.

(5) Yamaoka, T.; Yokoyama, S.; Omote, T.; Naitoh, K.; Yoshida, K. *J. Photopolym. Sci. Techn.* **1996**, *51*, 392. Yamaoka, T.; Yokoyama, S.; Omote, T.; Naitoh, K. *J. Polym. Sci. Technol.* **1994**, *7*, 293.

(6) Triggle, A. M.; Shefter, E.; Triggle, D. G. *J. Med. Chem.* **1980**, *23*, 1442. Fossheim, R.; Joslyn, A.; Solo, A. J.; Luchowski, E.; Rutlege, A.; Triggle, D. J. *J. Med. Chem.* **1988**, *31*, 300. Wang, S. D.; Herbette, L. G.; Rhodes, D. G. *Acta Crystallogr., C* **1989**, *C45*, 1748. Palmer, R. B.; Andersen, N. H. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2173.

(7) (a) Bai, S. H.; Chen, Y. B. *Chem. Pharm. Prog.* **1999**, *23*, 17. (b) Whang, W. G. *Pharmacol. Res.* **1996**, *34*, 187. (c) Mason, R.; Mak, T.; Trumbore, W.; Mason, P. *Am. J. Cardiol.* **1999**, *84*, 16L. (d) Velena, A.; Zibers, J.; Durbus, G. *Cell. Biochem. Funct.* **1999**, *17*, 237. (e) Allanore, Y.; Borderie, D.; Lemarechal, H.; Ekindjian, O. G.; Kahan, A. *Am. J. Med.* **2004**, *116*, 595. (f) Ganafa, A. A.; Walton, M.; Eatman, D.; Abukhalaf, I. K.; Bayorth, M. A. *Am. J. Hyperthen.* **2004**, *17*, 743.

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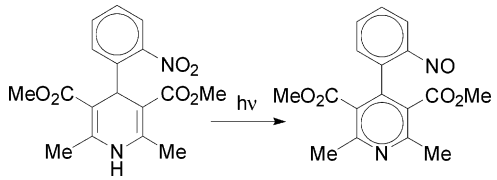
SCHEME 1



such as ischemia, arteriosclerosis, and stroke for their antioxidant activity.[7c−f] Most of these drugs bear a nitro group on the phenyl ring and thus contain both an easily oxidized and an easily reduced moiety in the same molecule, a fact that may have a bearing on their biological activity.[8a,b]

The donor−acceptor structure[8c] raises the question of whether an intramolecular redox reaction may occur, a step that may be easier under photochemical conditions. Actually, some drugs of this family are known to be photolabile and must be protected from light-exposure. The 2-nitrophenyl derivative nifedipine has been in use for a long time as a coronary vasodilator and is strongly photoreactive. This has motivated a series of photochemical and photobiologic studies showing that this compound is converted into the corresponding 2-nitrosophenylpyridine (Scheme 1),[9] a reaction that can be classed among the well-known intramolecular redox process of 2-nitrobenzyl derivatives,[10] and occurs both in solution and in the solid state. Whether a significant photodecomposition takes place in the skin after intake of the drug and a toxic effect results is a debated subject.[11]

2-Nitrophenyl derivatives are ill suited for the study of photoinduced electron-transfer processes because of the fast chemical reaction occurring. Better models can be found among the "second generation"[12] cardiac drugs, some of which contains the 3-nitrophenyl, rather than the 2-nitrophenyl, moiety. These have been found to be again photolabile, though at a lower degree,[13] but the available literature is mainly limited to the determination of the degradation kinetics in drug preparations.[14] It appeared to us that a more extensive study of the photochemistry of these molecules was warranted because (i) excitation may induce intramolecular electron transfer between two moieties held in a definite position, a topic actively investigated for a number of applications,[16] (ii) a better knowledge of the relatively little explored photochemistry of 3-nitrobenzyl derivatives[15] would be obtained, and (iii) a rationale for the photolability (and possibly the phototoxicity) of such drugs may be offered.

Results

Photoreactions. The compounds considered in this study were esters of the 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid. These were the dimethyl ester **1**, distinguished from nifedipine only by the position of the nitro group, the corresponding methyl ethyl ester **2**, the drug nitrendipine, as well as two derivatives containing a functional group in one of the ester alkyl chains, namely the isopropyl methoxyethyl ester **3** (nimodipine) and the methyl *N*-(methyl)-*N*-(benzyl)aminoethyl ester **4** (nicardipine). These compounds exhibit an absorption band in the near UV, with a maximum at ca. 350 nm (the tail extending in the visible results in a yellow color) and at ca. 230 nm. They are readily soluble in most organic solvents, but not in water, and most of the experiments were carried out in methanol and in acetonitrile, two solvents of differing hydrogen-donating ability. Irradiations were carried out at two wavelengths, 254 and 366 nm, corresponding to the two main band systems and under two conditions, air-equilibrated and argon-flushed solutions.

Irradiation of the dimethyl ester **1** under all of the above conditions gave a single product, as determined by HPLC monitoring. This was identified as the corresponding nitrophenylpyridine **5** by comparison with an authentic sample (Table 1, Scheme 2). At 50% conversion of **1**, product **5** was in every case ca. 70% of the consumed dihydropyridine. Likewise, both the methyl ethyl ester **2** and the methyl methoxyethyl ester **3** gave the nitro derivatives **6** and, respectively, **7**. With **3**, HPLC/MS analysis showed a minor peak by irradiation at 254 nm in Ar-flushed MeCN or MeOH, but not under different conditions, with MW corresponding to the nitroso analogue of compound **7** (**8**), which was not further investigated in view of the small amount.

In the case of the aminoethyl ester **4** the results were different, in that the corresponding nitrophenyl derivative (**9**, ca. 40% in MeCN and 20% in MeOH, both argon and air equilibrated) was accompanied by two further peaks. Separation by column chromatography after irradiation in acetonitrile allowed recognizing these as nitrophenyldihydropyridines in which the ester side was modified. Two products were obtained from chromatography, namely the *N*-benzyl and the *N*-benzyl-*N*-formyl derivatives (**10** and **11**, respectively, Scheme 3).

(8) (a) Schleifer, K. J. *J. Med. Chem.* **1999**, *42*, 2204. (b) Schleifer, K. J. *Pharmazie* **1999**, *54*, 804. (c) Compare Nelsen, S. F. In *Electron Transfer in Chemistry*; Balzani, V., Ed.; Wiley-VCH: Weinheim, 2001; Vol. 1, p 342.

(9) (a) Berson, J. A.; Brown, E. *J. Am. Chem. Soc.* **1955**, *77*, 447. (b) Thoma, K.; Kerker, R. *Pharm. Ind.* **1992**, *54*, 465. (c) Shim, S. C.; Pae, A. N.; Lee, Y. J. *Bull. Korean Chem. Soc.* **1988**, *9*, 271. (d) Pietta, P.; Rava, A.; Biondi, P. *J. Chromatog.* **1981**, *210*, 516. (d) Stasko, A.; Brazova, V.; Biskupic, S.; Ondrias, K.; Misik, V. *Free Rad. Biol. Med.* **1994**, *17*, 545. (e) de Vries, H.; Beijersbergen van Henegouwen, G. M. *J. Photochem. Photobiol. B: Biol.* **1998**, *43*, 217. (f) Buttafava, A.; Faucitano, A.; Fasani, E.; Albini, A. *Res. Chem. Intermed.* **2002**, *28*, 231. (g) Fasani, E.; Dondi, D.; Ricci, A.; Albini, A. *Photochem. Photobiol.* **2006**, *82*, in press.

(10) Barltrop, J. A.; Plant, P. J. *J. Chem. Soc., Chem. Commun.* **1966**, 827. Nurmukhametov, R. N.; Sergeev, A. M. *Zh. Fiz. Khim.* **1990**, *64*, 308. Walker, J. W.; Reid, G. P.; McCray, J. A.; Trentham, D. R. *J. Am. Chem. Soc.* **1988**, *110*, 7170.

(11) Al-Ajimi, H. S.; Dawe, R. S.; Renwick, A. G.; Macklin, B. S.; Ferguson, J.; Gibbs, N. K. *Photoderm. Photoim. Photomed.* **2000**, *16*, 111. Fujii, H.; Berliner, L. J. *Magn. Reson. Med.* **1999**, *42*, 691.

(12) Freedman, D. D.; Waters, D. D. *Drugs* **1987**, *34*, 578.

(13) Mei, Q.; Shang, P.; Zhao, D.; Zhou, G. *Zhongguo Yaoxue Zazhi* **1998**, *33*, 291.

(14) Mielcarek, J. *Acta Pol. Pharm.* **1995**, *52*, 59. Mielcarek, J. *Acta Pol. Pharm.* **1995**, *52*, 465. Jakobsen, P.; Mikkelsen, E.; Laursen, J.; Jensen, F. *J. Chromatograph.* **1986**, *374*, 383. Mielcarek, J. *Pharmazie* **1996**, *51*, 477.

(15) See, e.g.: Muralidharan, S.; Beveridge, K. A.; Wan, P. *J. Chem. Soc., Chem. Commun.* **1989**, 1426.

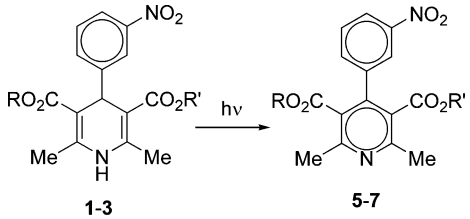
(16) Wegenwijs, B.; Verhoeven, J. W. *Adv. Chem. Phys.* **1999**, *106*, 221. Timberlake, L. D.; Morrison, H. *J. Am. Chem. Soc.* **1999**, *121*, 3618. Liu, G.; Heisler, L.; Li, L.; Steinmetz, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 11412. Osuka, A.; Noya, G.; Taniguchi, S.; Okada, T.; Nishimura, Y.; Yamazaki, I.; Mataga, N. *Chem. Eur. J.* **2000**, *6*, 33. Maruyama, K.; Osuka, A.; Mataga, N. *Pure Appl. Chem.* **1994**, *66*, 867. Kaplan, R. W.; Napper, A. M.; Waldeck, D. H.; Zimmt, M. B. *J. Am. Chem. Soc.* **2000**, *122*, 12039. Zhang, L. P.; Chen, B.; Wu, L. Z.; Tung, C. H.; Cao, H.; Tanimoto, Y. *Chem. Eur. J.* **2003**, *9*, 2763. Guo, X.; Zhang, D.; Zhang, H.; Fan, Q.; Xu, W.; Ai, X.; Fan, L.; Zhu, D. *Tetrahedron Lett.* **2003**, *59*, 4843. Miranda, M. A.; Lahoz, A.; Bosca, F.; Metni, M. R.; Abdelouahab, F. B.; Castell, J. V.; Perez-Prieto, J. *Chem. Commun.* **2000**, 2257. Le, T. P.; Rogers, J. E.; Kelly, L. A. *J. Phys. Chem A* **2000**, *104*, 6778. Levy, S. T.; Rubin, M. B.; Speiser, S. *J. Am. Chem. Soc.* **1992**, *114*, 10747. Pincock, J. A.; Rifai, S.; Stefanova, R. *Can. J. Chem.* **2001**, *79*, 63. Wagner, P. J.; El-Taliawi, G. M. *J. Am. Chem. Soc.* **1992**, *117*, 8325.

TABLE 1. Quantum Yield of Reaction and Products Formed in the Photolysis of dihydropyrines 1−4[a]

compd	conditions	Φ_r(Ar), products (%)	Φ_r(air), products (%)
1	MeOH, 254 nm	0.013, **5**[b]	0.013, **5**
	MeOH, 366	0.004, **5**	0.004, **5**
	MeCN, 254	0.003, **5**	0.003, **5**
	MeCN, 366	0.0006, **5**	0.0005, **5**
	MeCN, 366[c]	0.003, **5** (5), **12** (40), **13** (18), **14** (12)	
2	MeOH, 254	0.013, **6**	0.014, **6**
	MeOH, 366	0.005, **6**	0.005, **6**
	MeCN, 254	0.004, **6**	0.003, **6**
	MeCN, 366	0.0004, **6**	0.0005, **6**
3	MeOH, 254	0.021, **7**(70)[d]	0.022, **7**
	MeOH, 366	0.004, **7**	0.004, **7**
	MeCN, 254	0.004, **7** (50)[d]	0.003, **5**
	MeCN, 366	0.0006, **7**	0.0005, **7**
	MeCN, 366[c]	0.004, **7**[e]	
	EtOH, 366[f]	≤0.0005	
4	MeOH, 254	0.064, **9** (7), **10** (21), **11** (20)	0.048, **9** (12), **10** (20), **11** (21)
	MeOH, 366	0.018, **9** (16), **10** (18), **11** (21)	0.021, **9** (19), **10** (22), **11** (20)
	MeCN, 254	0.097, **9** (36), **10** (20), **11** (7)	0.083, **9** (37), **10** (18), **11** (7)
	MeCN, 366	0.027, **9**(43), **10** (17), **11** (8)	0.022, **9** (40), **10** (18), **11** (8)

[a] Quantum yields determined by HPLC at 15−25% conversion. Products distribution at ca. 50% conversion. [b] When not indicated, the product amounts to ca. 70% of the converted starting compound. [c] In the presence of 0.1 M triethylamine. [d] Product **7** was accompanied by a small amount of the nitroso analogue **8**, as indicated by HPLC analysis. [e] Product **7** was accompanied by the amino-, hydroxylamino-, and nitrosophenyl-1,4-dihydropyridines analoguous to products **12**−**14**, as indicated by HPLC/MS analysis. [f] In an EtOH glass at 77 K.

SCHEME 2



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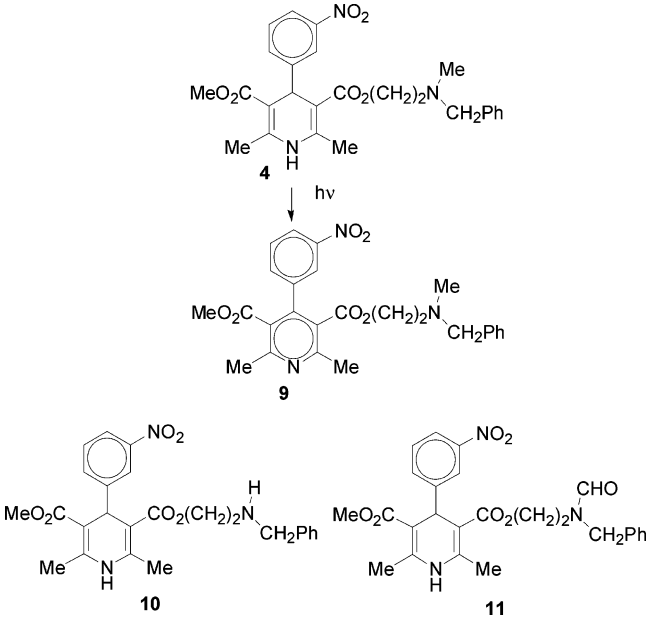
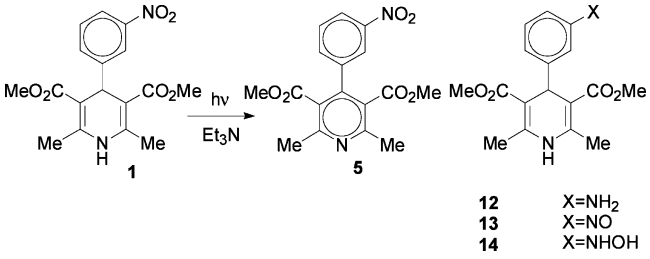


Separate experiments at 15−25% conversion of the starting material were carried out for the determination of the quantum yields of reaction (Φ_r) under the above conditions. The results are reported in Table 1.

SCHEME 4



Furthermore, irradiation in the matrix was carried out in the case of **4**. A solution in ethanol was degassed and brought to 90 K. Under these conditions, the absorption spectrum showed some changes, in that the bands around 360 and 280 nm acquired some structure and were red-shifted by ca. 10 nm. Prolonged irradiation at 366 nm under these conditions produced no change, demonstrating that $\Phi_r \leq 0.0005$.

In view of the low quantum yield of reaction of these dihydropyridines, it was deemed useful to determine whether the reaction might be more effective in the presence of a suitable additive. Positive results were obtained with triethylamine, and the conversion of both **1** and **3** was considerably faster when the amine was present at >0.01 M concentration. The product distribution was also changed, with the respective nitrophenylpyridines **5** and **7** now accompanied by some faster eluting products, one of which predominating. The result was more closely examined with **1**, where comparison with authentic standards showed that the main product at complete consumption of the starting compound was the aminophenyldihydropyridine **12** and the minor ones the corresponding nitroso and hydroxylamino derivatives **13** and **14** (Scheme 4).

Photophysical Data. Dihydropyridines **1**−**4** exhibited no detectable fluorescence at room temperature. They showed an intense yellow phosphorescence (but only a very weak fluorescence) in the matrix (EPA glass at 77 K) as reported in Table 2. As a representative example, the emission of **1** under these conditions is reported in Figure 1a. Addition of 10% triethylamine did not alter the emission.

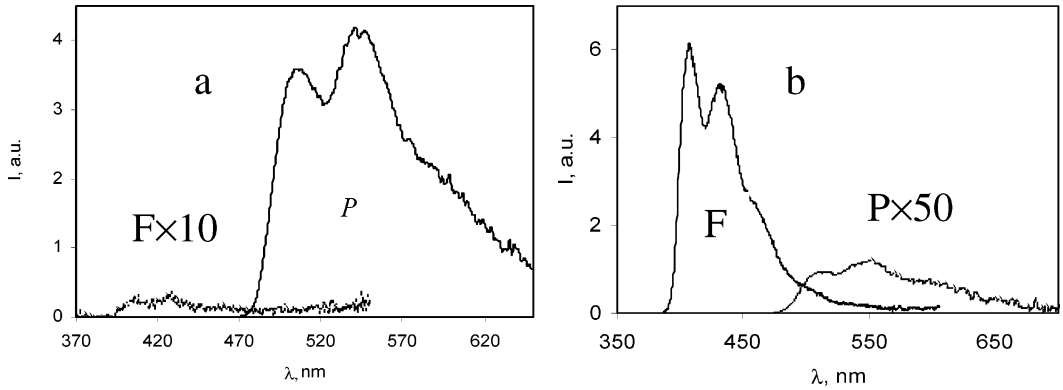


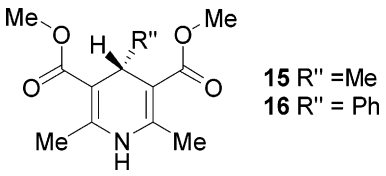
FIGURE 1. (a) Fluorescence (×10) and phosphorescence of compound **1** in EPA glass at 77 K. (b) Fluorescence and phosphorescence (×50) of compound **16** in EPA glass at 77 K.

TABLE 2. Data on the Luminescence from Dihydropridines 1−4, 15, and 16

	fluorescence			phosphorescence		
	295K[a]		77K[b]	77K[b]		
compd	λ_{max}, nm	Φ_f	Φ_f	λ_{max}, nm	Φ_p	E_T, kcal mol^{-1}
15	437 (5850)[a]	0.006	0.8	*c*		
16	439 (5790)[a]	0.005	0.8	516, 548	$<1 \times 10^{-3}$	60.2
1	*c*			513, 547	0.12	60.3
2	*c*			514, 545	0.11	60.3
3	*c*			514, 545	0.10	60.3
4	*c*			514, 547	0.10	59.6

[a] In acetonitrile; similar values in methanol; the Stoke's shift (cm^{-1}) is indicated in parentheses. [b] In EPA glass. [c] Not detected.

It appeared important to understand the role of the nitrophenyl moiety in determining the observed luminescence. Therefore we examined some analogues lacking this group, viz. the corresponding 2, 4, 6-trimethyl (**15**) and 2, 6-dimethyl-4-phenyldihydropyridines (**16**). As previously reported for related derivatives,[17] these exhibited a blue fluorescence (see Figure 1). This was rather weak in fluid solution ($\Phi_f \cong 5 \times 10^{-3}$, τ_f 0.3 ns for **15**, 0.15 ns for **16**). However, the emission became much more intense (Φ_f 0.8) and somewhat structured in EPA glass at 77K, while the lifetime became much longer (τ_f 8 ns, k_f 1.2×10^8 s^{-1} for both compounds).



The yellow phosphorescence characteristic of compounds **1**−**4** was barely detected for **16** (see Figure 2) and not at all for **15**. A sensitization experiment was attempted. Thus, a glass containing both naphthalene and **15**, under conditions in which most of the light was absorbed by the former, exhibited a phosphorescence spectrum resulting form the sum of the naphthalene phosphorescence and of a further weak emission. The latter had the same shape as that from the above phenyl derivatives (see Figure 3).

Nanosecond flash photolysis in acetonitrile solution evidenced no transient in the region 380−650 nm for any of the dihydropyridine considered above. However, flashing a naphthalene−**15** mixed solution in MeCN (under conditions where the former absorbed most of the light) showed that the naphthalene triplet was efficiently quenched by the dihydro-

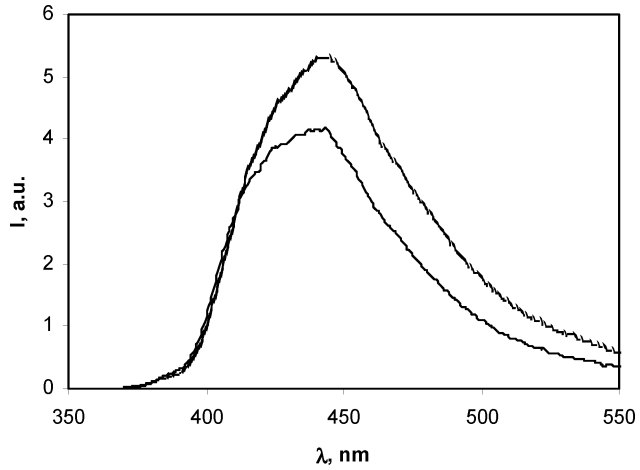


FIGURE 2. Fluorescence of compounds **15** (upper trace) and **16** in acetonitrile at 300K.

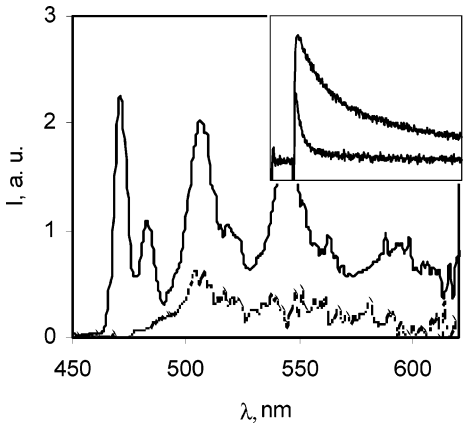


FIGURE 3. Phosphorescence from a mixed solution of naphthalene and compound **15** in EPA glass at 77 K (upper trace) and the spectrum resulting from subtraction of the naphthalene phosphorescence emission from the above curve (lower trace). The inset shows the decay of the 415 nm transient absorption resulting from flashing (266 nm) a naphthalene solution in acetonitrile (upper trace) as well as of an identical solution containing 2.3×10^{-3} M **15** (lower trace).

(17) Deme, A. K.; Lusis, V. K.; Dubur, G. Y. *Khim. Geterotsikl. Soedin.* **1987**, 67.

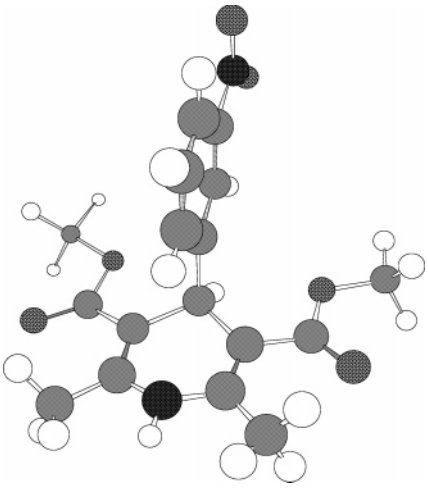


FIGURE 4. Optimized (B3LYP 6-31+G(d)) molecular structure of compound **1**.

pyridine (observed rate constant, 3.9×10^9 M^{-1} s^{-1}, see the inset in Figure 3).

Structure. To further document the behavior of these compounds, the conformations of the nitrophenyl derivative **1** were examined by the B3LYP method. The most stable conformer (in MeCN bulk) had a flattened boat structure (N and C_4 both over the plane, with torsion angles of 6 and 22°, see Figure 4). The esters groups were essentially coplanar with the ring double bonds; the phenyl group formed a 62° angle with the dihydropyridine ring and had the substitent *syn*-antiperiplanar to the C_4 hydrogen.[18] The most characteristic feature, however, was that several other conformers were located with an energy within 1 kcal mol^{-1} from the above structure. These differed for the *syn* or *anti* position of the 3′-nitrophenyl group and the orientation of the ester groups. One of the conformers corresponded to that present in the crystal state (see the Supporting Information). Thus, it was expected that easy equilibration occurred in solution and in fact NMR studies had ascertained that different conformers of **1** were present in solution.[18e]

Discussion

Excited States Involved. Nitrophenyldihydropyridines **1**−**4** contain two independent chromophores, the 1,4-dihydropridine-3,5-dicarboxylate, and the 3-nitrotoluene moieties, separated by a sp^3 carbon and will be indicated by the acronym PyH_2-PhNO_2 in the following. It is clear that the lowest singlet is localized on the dihydropyridine moiety. In fact, the long wavelength part of the absorption spectrum of **1**−**4** is quite similar to that of 4-unsubstituted and 4-alkyl-substituted analogues such as **15** (PyH_2-Me), where only this chromophore is present. The bands of **15** peak at ca. 350 nm (log $\epsilon \sim 4$), 250 (4.2), and 230 nm (4.35). This compound fluoresces in solution, and as one may expect from its push−pull structure (an enamino ester), the emission is characterized by a strong Stoke's shift (>5000 cm^{-1} in acetonitrile and methanol). The fluorescence is weak at room temperature, with a quantum yield lower than 0.01[19] and a short lifetime ($k_f > 3 \times 10^9$ s^{-1}). However, this is intense in EPA at 77 K where Φ_f approaches the unitary value and the observed rate constant, $k_f \sim 1 \times 10^8$ s^{-1}, corresponds to that expected for S_1 on the basis of the absorption spectrum (for the long-wavelength band. It has been calculated that $f \cong 0.1$[20] and the "natural" rate constant $k_f \cong 1 \times 10^8$ s^{-1}). Such a large temperature dependence of the fluorescence is reasonably due to the non rigid framework of the bis-enaminoester chromophore (see above and Figure 4). Equilibration between different conformers is fast (see the Supporting Information) and this introduces an efficient channel for non radiative decay. As a result, the experimental fluorescence lifetime at room temperature is dictated by internal conversion (i.e., $k_d^1 \sim 5 \times 10^9$ s^{-1}) in solution, while this mode is blocked in a rigid glass.

Introduction of the phenyl group in position 4 as the second chromophore is not expected to involve a major π interaction with the dihydropyridine moiety, in view of the large angle they form.[6] Indeed, as already remarked by Kurfürst,[20] the absorption spectrum of 4-phenyl derivative **16** (PyH_2-Ph) roughly corresponds to the sum of the spectrum of **15** and of that of benzene. Compound **16** exhibits the same temperature-dependent fluorescence as **15** with an identical shape of the spectrum (see Figure 2 and Table 2). Thus, with **16** the lowest excited singlet remains localized on the dihydropyridine moiety, as one would expect. The almost unitary value of Φ_f at 77 K indicates that this state undergoes very little (though non zero, since a weak phosphorescence can be appreciated, see Figure 1b) intersystem crossing in matrix, $k_{isc}/k_f \leq 1 \times 10^{-3}$.[21] The shape and position of phosphorescence exclude that it can be attributed to the nitrobenzene moiety and its similarity to that of fluorescence supports that it arises from a dihydropyridine localized triplet. The energy of this state is 60.2 kcal mol^{-1}. The fact that some phosphorescence is observed despite the inefficient ISC suggests that in glass emission is a major decay path from $^3PyH_2$-Ph, just as it occurs from the corresponding singlet in a matrix. Intersystem crossing is even less significant with 4-methyl derivative **15**, where no spontaneous phosphorescence is observed. However, the triplet must have a similar energy, as indicated by the fact that it can be reached through sensitization by naphthalene, E_T 60.5 kcal mol^{-1}. This is supported by quenching of the naphthalene triplet in solution (see Figure 3, inset) and observation of sensitized phosphorescence from **15** in the glass in the presence of naphthalene (absorbing >90% of the exciting light, see Figure 3).

In the 4-(3-nitrophenyl) derivatives **1**−**4** (PyH_2-$PhNO_2$) the phenyl ring remains askew (see Figure 4) and has no effect on the dihydropyridine localized S_1 state, as indicated by the close similarity of the long-wavelength part of the absorption spectrum to that of **15** and **16**. The fact that these compounds are virtually nonfluorescent, either at 295 or at 77 K (Φ_f in glass $\leq 1 \times 10^{-2}$), indicates that a new decay channel is involved. This can be reasonably proposed to be electron transfer from the dihydropyridine chromophore (E_{ox} +0.67 V vs $Ag/AgNO_3$ for

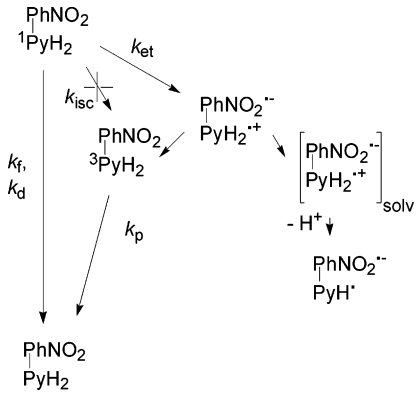
(18) (a) For a previous semiempirical MO conformational analysis, see ref 18b. For the molecular structure in the crystal state and in solution, see ref 18c−e. (b) Cotta-Ramusino, M.; Varì, M. R. *THEOCHEM* **1999**, *492*, 257. (c) Fossheim, R.; Svarteng, K.; Mostad, A.; Rømming, C.; Shefter, E.; Triggle, D. J. *J. Med. Chem.* **1982**, *25*, 126. (d) Rovnyak, G.; Andersen, N.; Gougoutas, J.; Hedberg, A.; Kimball, S. D.; Malley, M.; Moreland, S.; Porubcan, M.; Pudzianowski, A. *J. Med. Chem.* **1988**, *31*, 936. (e) Marubayashi, N.; Ogawa, T.; Hamasaki, T.; Hirayama, N. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1309.

(19) A previous study reported a much higher Φ_f value; however, see ref 17.

(20) Kurfürst, A.; Kuthan, J. *Collect. Czech. Chem. Commun.* **1983**, *43*, 1422.

(21) ISC must be even less significant at room temperature, where nonradiative decay cuts down the singlet lifetime.

SCHEME 5



15, +0.84 for **1** in acetonitrile)[22] to the nitrotoluene moiety (E_{red} −1.25 V, see Scheme 5). Taking into account the excitation energy, these values show that ET from $^1PyH_2$-$PhNO_2$ (E_S 73 kcal mol^{-1}) to $PyH_2^{\bullet+}-PhNO_2^{\bullet-}$ is largely exothermic.[23] The lack of fluorescence indicates that singlet deactivation through this channel is fast, $k_{et} \geq 1 \times 10^{10}$ s^{-1}.

On the other hand, compounds **1**−**4** phophoresce in glass at 77 K, and the emission has the same shape as the weak phosphorescence of **16** but is more intense by 2 orders of magnitude ($\Phi_p \approx 0.1$). The similarity of the vibrational structure to that of fluorescence supports that the emitting triplet is in any case localized on the dihydropyridine chromophore (while the nitrobenzene triplet is higher in energy[24] than the emitting state observed and is not expected to phosphoresce efficiently). The low Φ_p in compounds **15** and **16** proves that ISC between PyH_2-localized states (k_{isc} in Scheme 5) is inefficient, and thus, population of the $^3PyH_2-PhNO_2$ state in compounds **1**−**4** must involve an interaction with the nitrophenyl moiety (see Scheme 5). Indeed, back-electron transfer to give a localized triplet from the charge-separated state has been demonstrated in other tethered donor−acceptor dyads (D−A).[25] This requires that (one of) the localized triplets has a lower energy than the zwitterionic biradical $D^{\bullet+}-A^{\bullet-}$. This condition does not apply to the present case, since the energy of the emitting state is 60.2 kcal mol^{-1}, that is 13.3 kcal mol^{-1} above the $PyH_2^{\bullet+}-PhNO_2^{\bullet-}$ state in solution.[26]

However, in a frozen glass the zwitterion is less stabilized, due to difficult solvent reorganization and probably also of the hindering of the required intramolecular reorganization. Back-electron transfer to give a dihydropyridine localized triplet ($^3PyH_2-PhNO_2$, see Scheme 5) may thus be possible in glass, in analogy to what previously observed for other donor−acceptor dyads.[25] Importantly for this issue, Verhoeven and Paddon-Row showed that with some aniline-cyanonaphthalene dyads the CT fluorescence shifts to the blue in a frozen MTHF matrix, with an energy increase by as much as 17 kcal mol^{-1}.[26c]

Photoreactions. As it appears from Table 1, 4-(3-nitrophenyl)-1,4-dihydropyridines **1**−**3** react sluggishly (Φ_r 0.0005 to 0.02, compare with the 0.4 value observed for the 2-nitrophenyl analogues;[9c,g] see below for the more efficient reaction of **4**) and the isolated products (Scheme 2) result from a net oxidation involving aromatization of the dihydropyridine moiety, rather than disproportionation with reduction of the nitro group as with the 2-nitro isomer (Scheme 1). As shown in Table 1, compounds **1**−**3** react more efficiently at 254 than at 366 nm (by a factor of 3 to 10) and in methanol rather than in acetonitrile (again by a factor of 3 to 10); oxygen has a minimal effect. In the previous section, it was concluded that the relaxed zwitterionic biradical $PyH_2^{\bullet+}-PhNO_2^{\bullet-}$ is formed in solution.

Deprotonation of the radical cation of Hantzsch esters from the C_4 position is a favored process (path *a*, Scheme 6, the BDE is only 4.5 kcal M^{-1} as calculated through a thermochemical cycle).[27] This does not mean that the process is fast, however, at least when no proton acceptor is present. The difference between the present compounds and the 2-nitro isomers is that in the latter case a facile intramolecular proton transfer to the nitro group occurs[9] (indeed, the nitro group is suitably positionated over the plane of the dihydropyridine moiety). In the 3-nitro derivatives, proton transfer occurs only intermolecularly to the solvent (more efficiently with more basic methanol than with MeCN). This inefficient reaction is followed by stepwise oxidation of the resulting anion to the final products observed (Scheme 6, bottom).

A further path operates by irradiation at 254 nm, because the nitrobenzene chromophore ($\epsilon_{254} \approx 8000$ M^{-1} cm^{-1}) absorbs about a half of the light flux. As it is general with nitrobenzene derivatives, ISC is expected to be fast and formation of a nπ^* localized triplet ($PyH_2-{}^3PhNO_2$) competes with (exothermic) electron transfer from PyH_2 (path *b*, Scheme 6). Hydrogen

(22) Lopez-Alarcon, C.; Squella, J. A.; Miranda-Wilson, D.; Nunez-Vergara, L. J. *Electroanal.* **2004**, *16*, 539. Ogle, J.; Baumane, L.; Stradins, J.; Duburs, G.; Kadish, V.; Gavars, R.; Lusis, V. *Khim. Geterotsikl. Soedin.* **1985**, 1099.

(23) Calculated $\Delta G°$ for intramolecular electron transfer from the PyH_2 moiety in ^{1}**1** to the 3-nitrotoluene moiety $\Delta G°_{ET} = E°(D/D^{\bullet+}) - E°(A^{\bullet-}/A) - E_{exc} - e^2/\epsilon a = -26.1$ kcal mol^{-1}.

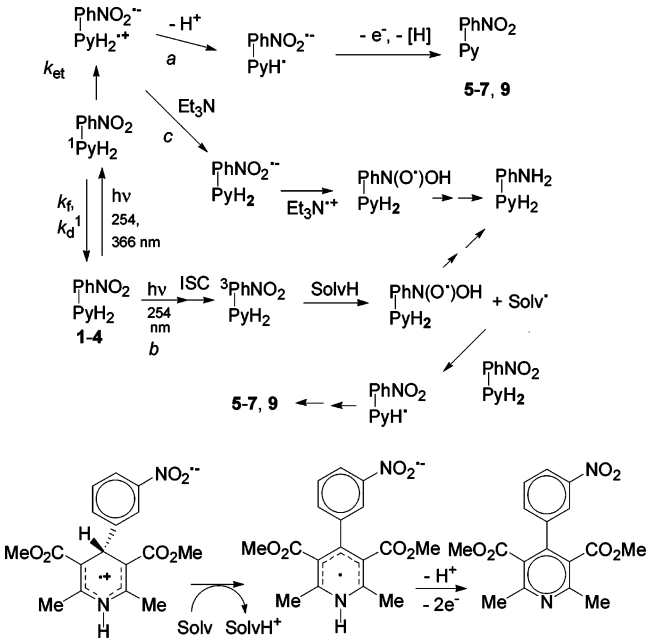
(24) For 3-nitrotoluene, E_T has been evaluated as >62.8 kcal mol^{-1}: Takezaki, M.; Hirota, N.; Terazima, M. *J. Phys. Chem. A* **1997**, *101*, 3443.

(25) (a) Gould, I. R.; Boiani, J. A.; Gaillard, E. B.; Goodman, J. L.; Farid, S. *J. Phys. Chem. A* **2003**, *107*, 3515. (b) Wiederrecht, G. P.; Svec, W. A.; Wasielewski, M. R.; Galili, T.; Levanon, H. *J. Am. Chem. Soc.* **1999**, *121*, 7726. (c) Wiederrecht, G. P.; Svec, W. A.; Wasielewski, M. R.; Galili, T.; Levanon, H. *J. Am. Chem. Soc.* **2000**, *122*, 9715. (d) Hasharoni, K.; Levanon, H.; Greenfield, S. R.; Gosztola, D. J.; Svec, W. A.; Wasielewski, M. R. *J. Am. Chem. Soc.* **1996**, *118*, 10228. (e) Davis, W. B.; Ratner, M. A.; Wasielwski, M. R. *J. Am. Chem. Soc.* **2001**, *123*, 7877. (f) Carbonera, D.; DiValentin, M.; Corvaja, C.; Agostini, G.; Giacometti, G.; Liddel, P. A.; Kuciauskas, D.; Moore, A. L.; Moore, T. A.; Gust, D. *J. Am. Chem. Soc.* **1998**, *120*, 4398. (g) Roth, H. D. *J. Phys. Chem. A* **2003**, *107*, 3432. (h) Levanon, H.; Galili, T.; Regev, A.; Wiederrecht, G. P.; Svec, W. A.; Wasielewski, M. R. *J. Am. Chem. Soc.* **1998**, *120*, 6366. (i) Rybtchinski, B.; Sinks, L. E.; Wasielewski, M. R. *J. Am. Chem. Soc.* **2004**, *126*, 12268. (j) Lewis, F. D.; Wu, Y.; Hayes, R. T.; Wasielwski, M. R. *Angew. Chem., Int. Ed.* **2002**, *41*, 3485. (k) Weiss, E. A.; Ahrens, M. J.; Sinks, L. E.; Gusev, A. V.; Ratner, M. A.; Wasielewski, M. R. *J. Am. Chem. Soc.* **2004**, *126*, 5577. (l) Lukas, A. S.; Wasielwski, M. R. *Molecular Switches* **2001**, 1. (m) Abad, S.; Pischel, U.; Miranda, M. A. *Photochem. Photobiol. Sci.* **2005**, *4*, 69. (n) Shulte, C. K.; Staerk, H.; Weller, A.; Werner, H. J.; Nickel, B. *Z. Phys. Chem.* **1976**, *101*, 371. Steiner, U. E.; Ulrich, T. *Chem. Rev.* **1989**, *89*, 51.

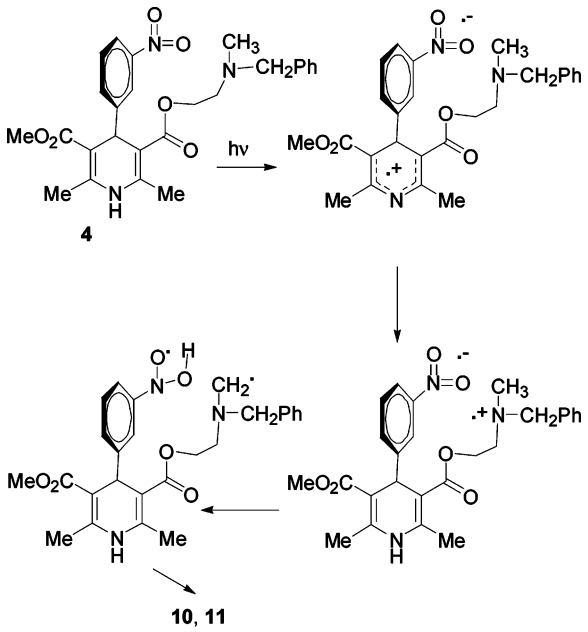
(26) (a) The free energy of the (solvent separated) zwitterionic biradical, i.e., the free energy difference between the charge-separated state and the reagent ground state is $\Delta G°_{SSRIP} = E°(D/D^{\bullet+}) - E°(A^{\bullet-}/A) + [(2.6\text{ eV}/\epsilon) - 0.13\text{ eV}]$, see ref 26b. Assuming that solvent stabilization occurs in the same way as with intermolecular examples, it can be calculated that for the $PyH_2^{\bullet+}-PhNO_2^{\bullet-}$ structure arising from **1**, $\Delta G°_{SSRIP} = 46.8$ kcal mol^{-1} in acetonitrile. Therefore, the free energy change for intersystem crossing from the charge separated state to the triplets localized on the dihydropyridine (E_T 60.2 kcal mol^{-1}) and on the nitrotoluene (E_T > 62.8 kcal mol^{-1}) moieties in **1** is endoergonic, $\Delta G°_{ET}$ = 13.3 and 15.9 kcal mol^{-1}, respectively. For previous cases of endoergonic formation of a localized triplet from a charge separated dyad in matrix, see, e.g. refs 25b ($\Delta G°_{ET}$ = 11.9 kcal mol^{-1}) and 26c. (b) Rehm, D.; Weller, A. *Isr. J. Chem.* **1970**, *8*, 259. (c) Goes, M.; Groot, M.; Koeberg, M.; Verhoeven, J. W.; Lokan, N. R.; Shepard, M. J.; Paddon-Row, M. N. *J. Phys. Chem. A* **2002**, *106*, 2129.

(27) Zhu, X. Q.; Li, H. R.; Li, Q.; Ai, T.; Lu, J. Y.; Yang, Y.; Cheng, J. P. *Chem. Eur. J.* **2003**, *9*, 871. Cheng, J. P.; Lu, Y.; Zhu, X.; Mu, L. *J. Org. Chem.* **1998**, *63*, 6108.

SCHEME 6



SCHEME 7



abstraction (compare nitrobenzene, $\Phi > 0.01$ in *i*-PrOH)[28] gives radicals Ph-N(O•)OH and Solv•, in turn abstracting hydrogen from the activated dihyropyridine positions. This finally leads to nitrophenylpyridines as the main products (ca. 70% yield; the accompanying reduction reasonably leads to—nondetected—anilinodihydropyridines, see Scheme 6). Aromatization of related dihydropyridines has been previously reported both by photosensitization, e.g., with 9-cyanophenanthrene, conjugated ketones, or onium salts,[29] and by reaction with radicals, including C-centered radicals (analogously to those from the solvent proposed here).[30]

Both the zwitterion and the localized triplet are expected to be short-lived (in the nanosecond order), in accord with the minimal oxygen effect on the above photoreactions (partial quenching of the triplet is probably compensated for by formation of active peroxyl radicals).[31]

Two reactions involving interaction with amines support the proposed scheme. Thus, irradiation of **1** in the presence of triethylamine leads to a moderate increase in the quantum yield of reaction as well as a change in the products formed. The new products conserve the dihyropyridine moiety intact and result from the stepwise reduction of the nitro group to nitroso, hydroxylamino, and amino groups. As indicated above, the excited singlet is short-lived ($\ll$1 ns), and thus the amine rather reacts with the zwitterion. The oxidation potential of tertiary amines is more positive than that of PyH_2 by a relatively small amount (ca. 0.1 V for Et_3N).[32] This fact, coupled with the known fast deprotonation of amine radical cations[33] and protonation of nitrobenzene radical anion,[34] suggests that sequential electron and proton transfer (path *c*, Scheme 6) may explain the observed reaction.

A second evidence is given by the reaction of (*N*-methyl-*N*-benzyl)aminoethyl ester **4**, which turns out to be much more reactive than compoounds **1** to **3** and undergoes oxidative cleavage of the alkylamino group in the side chain in a comparable proportion (from 30 to 80%) with oxidation of the dihydropyridine moiety. There is no difference either in the absorption spectrum or in the photophysics of this compound, thus the initial electron transfer between the two π systems occurs as in the previous cases. However, the flexible tether in this molecule makes the amino group able to interact with both chromophores, and as mentioned above, the oxidation potential of a tertiary amine is close to that of the dihydropyridine. A reasonable hypothesis is thus that a secondary ET step from the amino group ensues again, in this case intramolecularly. The mobility of this moiety allows interaction with the nitro group and thus intramolecular proton transfer as indicated in Scheme 7. Consistent with this shuttle mechanism, this reaction is much more efficient (Φ_r 0.05 to 0.1) than the sluggish proton transfer to the medium and the quantum yield is independent of the solvent nature. However, the difference between the two irradiation wavelengths remains, since the amine also quenches the $PhNO_2$ localized triplet state formed at 254 nm, again adding a further photoreduction path (compare the photoreduction of nitrobenzene by amines).[35] Noteworthy, compound **4** is virtually photostable when irradiated in glass at 77 K. Again, this well fits with the about proposal and the importance of conformation in inducing intramolecular hydrogen transfer.

(28) Döpp, D. In *Handbook of Organic Photochemistry and Photobiology*; Horspool, W. M., Song, P. S., Eds.; CRC, Boca Raton: 1994; p 1019. Hurley, R.; Testa, A. C. *J. Am. Chem. Soc.* **1966**, *88*, 4330.

(29) Taraban, M. B.; Kruppa, A. I.; Polyakiv, N. E.; Leshina, T. V.; Lusis, V.; Muceniece, D.; Duburs, G. *J. Photochem. Photobiol. A: Chem.* **1993**, *73*, 151.

(30) López-Alarcón, C.; Navarrete, P.; Camargo, C.; Squella, J. A.; Núñez-Vergara, L. J. *Chem. Res. Toxicol.* **2003**, *16*, 208. Núñez-Vergara, L. J.; López-Alarcón, C.; Navarrete-Encina, P. A.; Atria, A.; Camargo, C.; Squella, J. A. *Free Radical Res.* **2003**, *37*, 109.

(31) Valenzuela, V.; Santander, P.; Camargo, C.; Squella, J. A.; López-Alarcón, C.; Núñez-Vergara, L. J. *Free Radical Res.* **2004**, *38*, 715.

(32) Yasui, S.; Tsujimoto, M.; Itoh, K.; Ohno, A. *J. Org. Chem.* **2000**, *65*, 4715.

(33) Dombrowski, G. W.; Dinnocenzo, J. P.; Zielinski, P. A.; Farid, S.; Wosinska, Z. M.; Gould, I. R. *J. Org. Chem.* **2005**, *70*, 3791.

(34) Metcalfe, R. A.; Waters, W. A. *J. Chem. Soc. B* **1969**, 918.

(35) Sundararajan, K.; Ramakrishnan, V.; Kuriacose, J. C. *Ind. J. Chem.* **1983**, *22B*, 257. Sundararajan, K.; Ramakrishnan, V.; Kuriacose, J. C. *Ind. J. Chem.* **1984**, *23B*, 1086. Döpp, D.; Müller, D.; Seiler, K. H. *Tetrahedron Lett.* **1974**, 2137.

Conclusion

The two separate chromophores contained in 4-(3-nitrophenyl)-substituted Hantszch dihydropyridines (PyH_2-PhNO_2) exhibit an opposite photochemistry. The dihydropyridine chromophore decays radiatively both from the singlet and from the triplet, whereas the short-lived 3-nitrotoluene moiety does not emit and abstracts hydrogen inefficiently, mainly decaying by internal conversion. Both the lowest singlet and the lowest triplet are localized on the PyH_2 chromophore but spontaneous ISC within this moiety is negligible. On the basis of luminescence data, it is suggested that short path (6 Å) intramolecular electron transfer occurs efficiently in this dyad. In solution, the zwitterion undergoes inefficient deprotonation finally resulting in aromatization of the pyridine ring. In the presence of an amine, or more efficiently of a tethered amino group, hydrogen transfer to the nitro group rather occurs. This is revealed by the formation of aminophenyldihydropyridines in the first case and by the oxidation of the side-chain in the latter one. In glass a 77 K the zwitterion is less stabilized and back electron transfer leads the otherwise inaccessible (and phosphorescing) $^3PyH_2-PhNO_2$ state.

This solution mechanism rationalizes the photolability of 3-nitrophenyl substituted dihydropyridine cardiac drugs and the intervention of radicals in it suggests that these drugs may have a phototoxic effect. Likewise, the radical path offers an explanation for the use of related molecules for cross-linking photosensitive polymers.

The photophysics of these molecules is of interest because of the short-path electron transfer between the two π systems in a known configuration. This may be taken as a model for the photochemical events in *intermolecular* exciplexes. It is reasonable to expect that changing the reduction potential of the aryl group in 4 it is possible to modulate the extent of charge transfer in aryldihyropyridines, conspicuously revealed by the disappearance of the blue florescence and the appearance of a yellow phosphorescence when an electron accepting group opens a path for ISC. Moreover, the results with the methylaminoethyl ester **4** support that the chemistry can be varied through a further intramolecular mediation. Thus, the present PyH_2-PhNO_2 dyads may be further developed into more complex structures for predetermined electron transfer, in view of the interest for this topic (e.g., for modeling photosynthesis,[25h,i] studying DNA-mediated electron transfer,[25j] and building molecular wires[25k] or molecular switches).[25l] The easy synthesis and large possibility variation of each molecular feature in Hantzsch esters (aromatic substituent in **4**, ester alkyl chain, introduction of further groups, synthesis of oligomeric structures) suggest that this class of molecules could be explored for building a range of simple, metal-free, systems where electron transport occurs and may find applications. Work toward this target is underway.

Experimental Section

General Methods. Samples of dihydropyridines **2**−**4** were kindly supplied by the firm Lusochimica, Milan. Compound **15** was of commercial origin, and compounds **1** and **16** were prepared by conventional procedures.[36] Samples of nitrophenylpyridines **5**, **9**,[37] **6**, and **7**[38] for comparison with the photoproducts were prepared according to published procedures. Samples of phenyldihydropyridines **12**−**14** for comparison with the irradiation products of **1** in the presence of triethylamine were prepared by reduction of compound **1** through literature procedures.[39] *N*-Benzyl-2-aminoethyl methyl 1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (**11**) showed spectroscopic properties identical to those reported in the literature.[40]

Photochemistry. Small-scale experiments were carried out on 2 mL samples of 5×10^{-4} M solutions of the dihydropyridines in MeCN or MeOH in spectrophotometric couvettes after argon flushing and addition of triethylamine when appropriate. These were irradiated by means of 15 W low-pressure mercury arcs (254 nm) or 15 W phosphor-coated lamps (center of emission 366 nm, mid-height width 35 nm), and the course of the reaction was monitored by HPLC by using a C-18 inverse phase column and eluting with methanol−water mixtures. The light flux was measured by ferrioxalate actinometry.

In the irradiation of compound **1** in the presence of 0.1 M triethylamine, the photolyzed solutions were examined by HPLC/MS and the peaks of products **12**−**14** were recognized by comparison with authentic samples prepared as above.

Preparative experiments were carried out on 300 mL portions of $5 \times 10\ M^{-3}$ solutions of the dihydropyridines in an immersion well apparatus after argon flushing. These were internally irradiated by means of a 150 W medium-pressure mercury arc through Pyrex until a ca. 80% conversion was reached (HPLC). Evaporation of the solvent and chromatography afforded the photoproducts reported in Table 1, which were recognized by comparison of their properties, in particular HPLC (RP-18 endcapped column, MeOH/H_2O 7/3 mixture as eluant) and NMR, with authentic samples prepared as above. In the case of nimodipine (**3**), a minor peak with t_R 24.0 min and *m*/*z* 400, as expected for the corresponding nitrosophenylpyridine **8**, was detected but not further investigated. In the case of nicardipine **4**, products **10** and **11**[40] were formed, besides aromatized **9**.

***N*-Benzyl-*N*-formyl-2-aminoethyl methyl 1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (11):** whitish powder; mp 84−85 °C; ^1H NMR ($CDCl_3$, 50 °C, some of the peaks are split due to hindered rotations; when this occurs the more intense one is indicated) δ 2.4 (s, 3H), 2.45 (s, 3H), 3.4 and 3.5 (two m, 2H), 3.7 (s, 3H), 4.2 (m, 2H), 4.3 and 4.5 (AB, 2H), 5.1 (s, 1H), 6.2 (s, 1H), 7.3 (m, 5H), 7.7 (d, 1H), 8.0 (m, 1H), 8.1 (m, 2H), 8.25 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 19.3 (CH_3), 19.6 (CH_3), 39.3 (CH_3), 44.9 (CH_2), 50.7 (CH), 51.1 (CH_2), 59.8 (CH_2), 120.1 (CH), 120.5 (CH), 122.7 (CH), 123.5 (CH), 126.5 (CH), 126.9 (CH), 127.3 (CH), 127.6, 127.7 (CH), 128.3, 133.7 (CH), 144.4, 145.5, 147.9, 149.2, 162.5 (CH), 166.2, 167.0; IR (neat) ν 3310, 1705, 1550, 1500 cm^1. Anal. Calcd for $C_{26}H_{27}N_3O_7$: C, 63.28; H, 5.51; N, 8.51. Found: C, 63.4; H, 5.7; N, 8.2.

Luminescence. The luminescence was measured either at room temperature or at 77K by means of a fluorimeter. Quantum yields of emission were measured taking quinine bisulfate ($\Phi_f = 0.546$ at room temperature) or carbazole (in glass, $\Phi_p = 0.24$)[42] as a standard. The fluorescence lifetime was measured through the single-photon counting technique.

Calculations. All calculations were carried out by using the Gaussian 2003 program package (see the Supporting Information). All the geometric structures of the reactants and transition states located were fully optimized both in the gas phase and in acetonitrile

(36) Carabateas, P. M.; Brundage, R. P.; Gelotte, K. O.; Gruett, M. D.; Lorenz, R. R.; Opalka, C. J. J.; Singh, B.; Thielking, W. H.; Williams, G. L.; Lesher, G. Y. *J. Heterocycl. Chem.* **1984**, *21*, 1849.

(37) Shibanuma, T.; Iwanami, M.; Fujimoto, M.; Takanaka, T.; Murabami, M. *Chem. Pharm. Bull.* **1980**, *28*, 2609.

(38) Boecher, R. H.; Guengerich, F. P. *J. Med. Chem.* **1986**, *29*, 1596.

(39) Santander-Gimenez, I. P.; Nunez-Vergara, L. J.; Squella, J. A.; Navarrete-Encina, P. A. *Synthesis* **2003**, 2781. Simonič, I.; Stanovnik, B. *J. Heterocycl. Chem.* **1997**, 1725. Anana, R. D.; Ng, H.; Howlett, S. E.; Knaus, E. E. *Arch. Pharm.* **1997**, *330*, 53.

(40) Iwanami, M.; Shibamura, T.; Fujimoto, M.; Kawai, R.; Tanazawa, T.; Takahashi, K.; Murakami, M. *Chem. Pharm. Bull.* **1979**, *27*, 1426.

(41) Meyer, H.; Wehinger, E.; Bossert, F.; Scherling, D. *Arzneim. Forsch./Drug Res.* **1983**, *33*, 106.

(42) Bonesi, S. M.; Erra-Balsells, R. *J. Luminesc.* **2001**, *93*, 51.

solution using the hybrid density functional B3LYP with the 6-31+G(d) basis set. The optimization of the stationary points in the solvent bulk was calculated by using Gaussian 03 with the method B3LYP-6-31G(d)/CPCM with the standard setting for acetonitrile (see the Supporting Information).

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Supporting Information Available: Optimized molecular structure of the low energy conformers of compound **1** (B3LYP 6-31+G(d) method, torsion angles and atom coordinates supplied). This material is available free of charge via the Internet at http://pubs.acs.org.

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