Structure of the dimers arising from one-electron electrochemical reduction of pyridinium salts 3,5-disubstituted with electron-withdrawing groups

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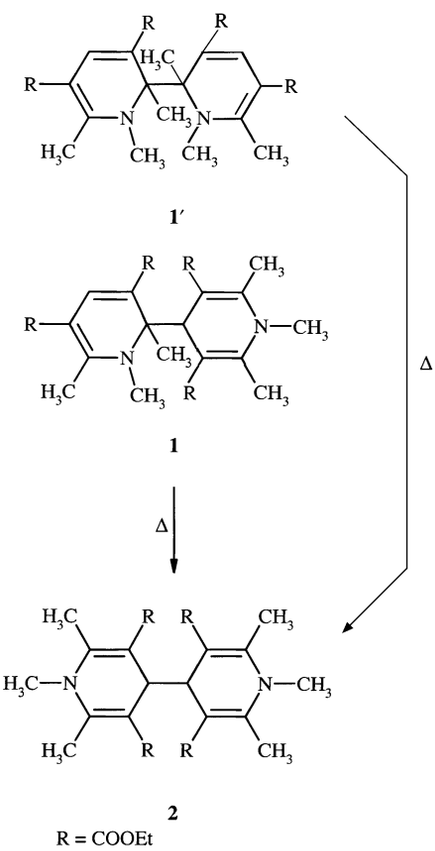
One-electron electrochemical reduction of the salts 1-benzyl-3,5-bis(methylcarbamoyl)pyridinium bromide **3a** and 1-benzyl-3,5-dicarbamoylpyridinium bromide **3b** yields mixtures of four isomeric dimers, as shown by HPLC analysis and mass spectrometry. ^{1}H and ^{13}C NMR spectrometry allows us to determine the structures of the mixture components. In both mixtures, the two most abundant products are identified as 4,4′- and 2,4′-tetrahydrobipyridines (**5a**, **5b** and **6a**, **6b**, respectively), while minor amounts of a pair of diastereomeric 2,2′-linked dimers are also detected in (**7a**, **8a** and **7b**, **8b** respectively). Therefore, the NMR studies lead to the conclusion that the structure assignment of conformers of **5a**, made previously for **6a** and **7a**, is not correct. All the 2,2′- and 2,4′-linked dimers undergo photochemical dissociation into two pyridinyl radicals which recombine to yield 4,4′-linked dimers.

Introduction

Several papers dealing with studies on the dimerization of pyridinyl radicals, generated by one-electron reduction of pyridinium salts 3-substituted with electron-withdrawing groups, have been published.[1] For example, dimer formation by electrochemical reduction of coenzymes NAD^+ and $NADP^+$ and their models has been extensively investigated,[2] and specific work has been devoted to elucidation of the role of steric and electronic factors in the regio- and stereoselectivity of the dimerization.[3] On the other hand, there are in the literature few reports on dimer formation by reduction of pyridinium salts 3,5-disubstituted with electron-withdrawing groups. Mumm *et al.*,[4] by treatment of the 3,5-bis(ethoxycarbonyl)-1,2,6-trimethylpyridinium salt with sodium amalgam, obtained a product to which they assigned the structure of the 2,2′-linked dimer **1′** (Scheme 1). Dimer **1′**, upon heating, underwent rearrangement to a higher-melting 4,4′-linked dimer **2** (Scheme 1). Much later, Huyser and co-workers, from the electrochemical reduction of the same salt, obtained the lower-melting dimer **1**,[5] which upon heating rearranged to dimer **2**. NMR analysis confirmed for **2** the structure of a 4,4′-linked dimer, but allowed them to correct the structure of the lower-melting dimer to that of the 2,4′-linked structure **1**. In a recent paper,[6] Leprêtre *et al.* reported that, by one-electron electrochemical reduction of the 1-benzyl-3,5-bis(methylcarbamoyl)pyridinium salt **3a** (Scheme 2), they obtained a mixture of three compounds, two of which were quantitatively transformed into the third, more stable, component by irradiation with a xenon lamp. The said authors claimed that, on the basis of NMR analysis, the structure of 4,4′-linked dimer **5a** (Scheme 2) has to be assigned to the stable compound, and the same structure it also is to be ascribed to the unstable compounds, which, therefore, have to be considered conformers of such a structure. These surprising findings prompted us to carry out a careful investigation of the dimers arising from one-electron electrochemical reduction of pyridinium salts **3a** and **3b** (Scheme 2). In our hands the reduction of both **3a** and **3b** yielded, as shown by analytical HPLC, mixtures of four compounds, to which accurate ^{1}H and ^{13}C NMR analysis and mass spectrometry allowed us to assign the dimeric structures **5a**, **6a**, **7a**, **8a** and **5b**, **6b**, **7b**, **8b**, respectively (Scheme 2). Furthermore,



Scheme 1

anaerobic photocatalysed isomerization of **6a**,**b**, **7a**,**b** and **8a**,**b** into **5a**,**b** was observed.

Results and discussion

Electrolysis of pyridinium salt **3a**, carried out in the dark, consumed one electron per mole of salt and gave a crude mixture which displayed an analytical HPLC profile (Fig. 1a, b) showing

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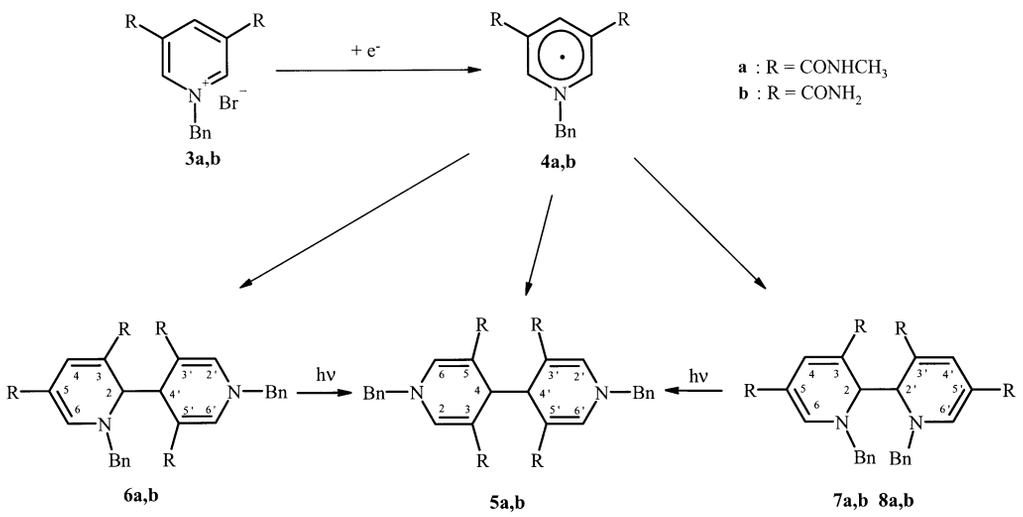
Table 1 ^{13}C NMR chemical shifts (δ ppm) of 2,2′- and 4,4′-linked dimers[a]

	C_2	C_3	C_4	C_5	C_6	NCH_2	CH_3	C=O
5a	135.61 d	107.05 s	38.89 d	107.05 s	135.61 d	56.78 t	25.40 q	168.31 s
5b	139.56	107.78 s	40.09 d	107.78 s	139.56	58.72 t	—	173.48 s
7a	57.61 d	104.64 s	[b]	113.33 s	144.52 d	59.27 t	25.27q	166.23 s
							29.08 q	167.38 s

[a] DMSO-d_6; in spectra of compounds **5a** and **7a**, the aromatic carbon signals are in the regions δ_C 127.70–128.71 and 126.06–127.45, respectively; in the spectrum of compound **5b**, the aromatic carbon signals are in the region 128.63–130.94. [b] Signals obscured by the aromatic C signals.



Scheme 2

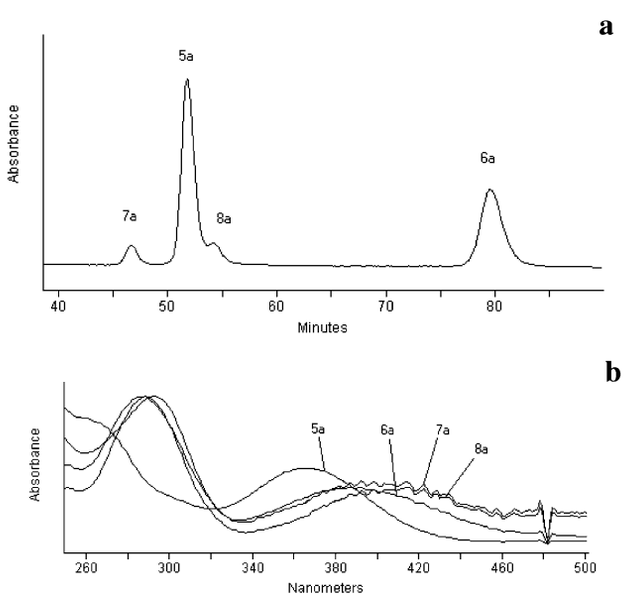


Fig. 1 (a) HPLC elution profile of crude mixture obtained from the reduction of salt **3a**. The eluate was monitored at 275 and 380 nm. Retention times (t_R) start from injection point. (b) UV spectra were recorded on the top of the corresponding chromatographic peaks and are normalized with respect to their own λ_{max}.

two main and two secondary peaks, according to the following sequence: I (t_R 46.5 min), II (t_R 52 min), III (t_R 54 min) and IV (t_R 79.5 min). Separation of components I, II and IV was performed by preparative HPLC, whereas component III, owing to its high lability to light, could not be isolated. I, II and IV were identified by mass spectrometry as dimers formed by the coupling of the radical **4a** (Scheme 2) arising from electrolysis. The symmetric structure of both I and II was clearly shown from the presence in their ^{1}H and ^{13}C NMR spectra of only eighteen proton signals and only sixteen carbon peaks respectively. In detail, five aromatic, two benzyl, two olefinic, six methyl, one methine and two amide hydrogens were easily detectable as well as six aromatic, four ring olefinic, two carbonyl, one N-benzylic, one methine and two methyl carbons (Tables 1 and 3). Furthermore, as regards I, the chemical shift of methine protons and carbons (δ 4.81 and δ_C 57.61, respectively), clearly indicated their position next to the ring nitrogen atom [1c,2a] and, therefore, allowed us to certainly identify I as a 2,2′-linked dimer. As regards II, the chemical shifts of methine protons and carbons (δ 3.82 and δ_C 38.89, respectively) unambigously indicated the positions 4 as the dimer-junction sites [1c,2,3] and, consequently, permitted us to identify II as a 4,4′-linked dimer. On such results the structures **7a** and **5a** were assigned to I and II, respectively (Scheme 2).

The complexity of the ^{1}H and ^{13}C NMR spectra (thirty-six proton signals and thirty-two carbon peaks) (Tables 2 and 4) strongly suggested an asymmetric dimeric structure for compound IV. In fact, by comparison with the ^{1}H and ^{13}C spectra of **5a** and **7a**, the presence in IV of both 1-benzyl-3,5-bis-(methylcarbamoyl)1,2- and -1,4-dihydropyridine moieties was certainly detected. Significatively, the presence of two methine hydrogens at δ 4.45 and 4.04 and two methine carbons at δ_C 61.01 and 38.96 clearly indicated the positions 2 and 4 as dimer-coupling sites, thus showing that IV was a 2,4′-linked dimer, consistent with the structure **6a** (Scheme 2).

Careful ^{1}H and ^{13}C NMR analyses, carried out on the isolated dimers **5a**, **6a** and **7a**, made easier the identification of the fourth, not isolable, component III. The ^{1}H NMR spectrum of the crude reduction mixture displayed, besides the proton signals of **7a**, a parallel series of eighteen peaks (Table 3), which was indicative of the same structural pattern, thus confirming the presence of another 2,2′-linked dimer, consistent with the structure **8a**. This structure was also confirmed by the UV spectrum, quite superposable on that of **7a** (Fig. 1b), both spectra being consistent with the chromophore systems of 3,5-dicarbamoyl-substituted 1,2-dihydropyridines.[7] Therefore, **7a** and **8a** were identified as a pair of diastereomers with respect to the C2–C2′ stereochemistry.

Table 2 ^{13}C NMR chemical shifts (ppm) of 2,4′-linked dimers.[a]

	C_2	C_3	C_4	C_5	C_6	$C_{2'}$	$C_{3'}$	$C_{4'}$	$C_{5'}$	$C_{6'}$	NCH_2	$N'CH_2$	CH_3	C=O
6a	61.01 d	108.43 s	[b]	113.23 s	146.23 d	137.20 d	103.41 s	38.96 d	106.89 s	135.03 d	57.57 t	59.66 t	25.51 q; 25.26 q	169.96 s; 167.26 s; 167.06 s; 166.15 s
6b	61.99 d	103.24 s	128.58 d	106.98	150.85 d	140.70 d	108.08 s	39.17 d	113.34 s	139.05	59.67 t	61.79 t		173.85 s; 172.44 s; 171.96 s; 171.60 s

[a] DMSO-d_6; in the spectra of compounds **6a** and **6b**, the aromatic carbon signals are in the regions δ_C 125.00–129.5 and 123.00–128.00, respectively. [b] Signals obscured by the aromatic C signals.

Finally, thorough ^1H NMR analysis of each of the four isomeric dimers allowed us to determine the following relative abundances from the ^1H NMR spectrum of the crude reduction mixture: **5a** 53%, **6a** 36%, **7a** 6%, **8a** 5%.

Monitoring by HPLC of the crude reduction mixture exposed to UV-light (254 nm), under anaerobic conditions, showed the gradual conversion of **6a**, **7a** and **8a** into **5a**: the transformation of **7a** and **8a** was complete in a short time, whereas, after 120 min, just 60% of the isomerization of **6a** had occurred (Fig 2a, b).

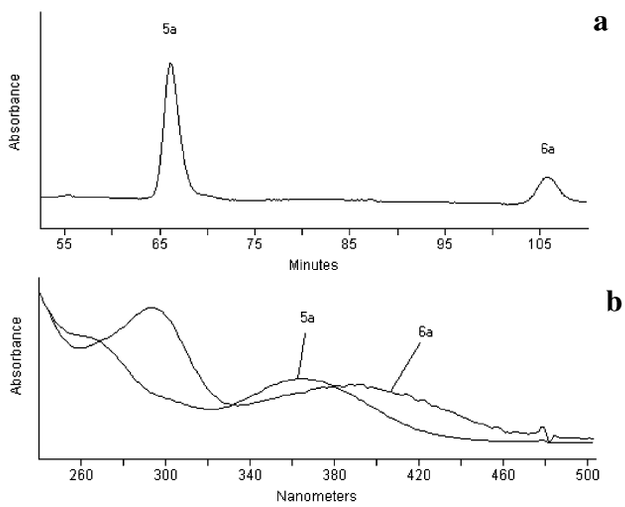


Fig. 2 (a) HPLC elution profile of dimer mixture from the reduction of salt **3a** after 120 min of exposure to UV light. The eluate was monitored at 275 and 380 nm. Retention times (t_R) start from injection point. (b) UVspectra were recorded on the top of the corresponding chromatographic peaks and are normalized with respect to their own λ_{max}.

As shown in the analytical HPLC elution profile reported in Fig. 3a, four products were also found in the mixture arising from the one-electron electrochemical reduction of salt **3b**. The four components were eluted according to the following order I (t_R 6.5 min), II (t_R 9.2 min), III (t_R 10.3 min) and IV (t_R 11.5 min). Owing to the high lability to light of I and III, only the major components II and IV were isolated by preparative HPLC. Their ^1H and ^{13}C NMR spectra were completely comparable, except for the missing NCH_3 resonances, with the corresponding spectra of **5a** and **6a** (Tables 1–4). Therefore, to II and IV have to be assigned the structures of 4,4′-linked dimer **5b** and 2,4′-linked dimer **6b**, respectively (Scheme 2). The same parallelism could be observed between the NMR hydrogen signal sequences and UV spectra of **7a** and **8a** and those of I and III (Table 3 and Fig. 3b), which were thus identified as a pair of diastereomeric 2,2′-linked dimers, consistent with the structures **7b** and **8b** (Scheme 2). Again. the complete ^1H NMR analysis of each of the four isomeric dimers allowed us to evaluate the following relative abundances from the ^1H NMR spectrum of the crude reduction mixture: **5b** 49%, **6b** 40%, **7b** 4.5%, **8b** 6.5%.

In this case as well, exposure of the crude reduction mixture to UV-light (254 nm), in the absence of air, produced the gradual transformation of **6b**, **7b** and **8b** into **5b**: both **7b** and **8b** were totally converted after few min, whereas, after 100 min, only a 50% of isomerization of **6b** was observed (Fig. 4a, b).

The results reported in this paper show that the dimerization of both the radicals **4a** and **4b** gives rise to formation of all four dimers theoretically possible: in fact, only one compound is to be expected as regards the 4,4′-linked dimers because of their molecular simmetry, as well as only one compound (a racemate) for the single asymmetric carbon of the 2,4′-linked dimers, whereas two diastereomers (a racemate and a mesoform) are consistent with the two equivalent asymmetric carbons of the 2,2′-linked dimers.

Table 3 ^{1}H NMR chemical shifts (δ ppm) and coupling constants (J Hz) of 2,2′-and 4,4′-linked dimers[a]

				NCH_2								
	H_2	H_4		H_6	H^a	H^b	NH	CH_3	NH_2	$J_{4,6}$	$J_{(CH_2NH)}$	$J_{a,b}$
5a	6.98 s	3.82 s		6.98 s		4.41 s	6.61 m	2.73 d				
7a	4.81 s	7.14 d	or	7.13 d	4.49 d	4.57 d	6.53 m	2.75 d		1.45	4.65	15.40
							6.29 m	2.77 d			5.00	
8a[b]	4.74 s	7.16	or	7.15	4.87 d	4.53 d		2.65 d[c]				15.90
5b	6.90 s	3.96 s		6.90 s		4.43 s			6.74			
7b[b]	4.74 s	7.10 d	or	7.07 d	4.68 d	4.51 d						15.80
8b[b]	[d]	7.09 s	or	7.06s	[d]	[d]						

[a] DMSO-d_6; in the spectra of compounds **5a**, **7a** and **8a**, the aromatic proton signals are in the regions δ 7.29–7.47 and δ 7.29–7.50, respectively; in the spectra of compounds **5b**, **7b** and **8b**, the aromatic proton signals are in the regions δ 7.23–7.39 and δ 7.20–7.49, respectively. [b] Chemical-shift values measured in the spectra of crude reduction mixtures of salts **3a** and **3b**. [c] Signal obscured by CH_3 signal of compound **5a**. [d] Signal obscured by NCH_2 signal of compound **6b**.

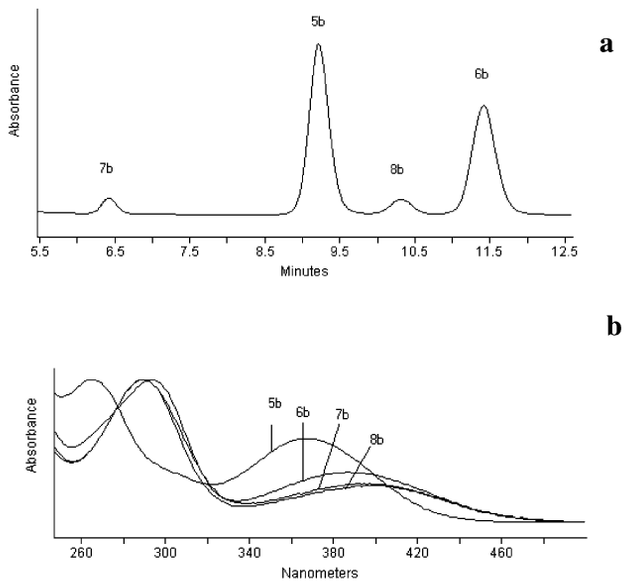


Fig. 3 (a) HPLC elution profile of crude mixture obtained from the reduction of salt **3b**. The eluate was monitored at 275 and 380 nm. Retention times (t_R) start from injection point. (b) UV spectra were recorded on the top of the corresponding chromatographic peaks and are normalized with respect to their own λ_{max}.

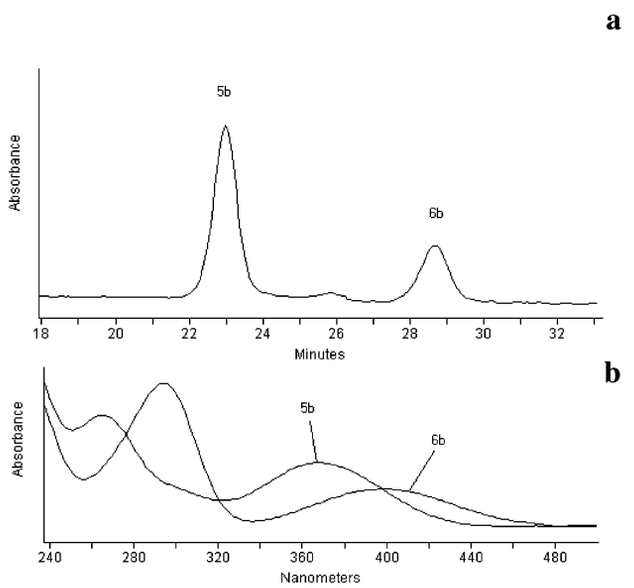


Fig. 4 (a) HPLC elution profile of dimer mixture from the reduction of salt **3b** after 100 min of exposure to UV light. The eluate was monitored at 275 and 380 nm. Retention times (t_R) start from injection point. (b) UV spectra were recorded on the top of the corresponding chromatographic peaks and are normalized with respect to their own λ_{max}.

The clear predominance (about 70%), among the reduction products of salts **3a** and **3b**, of dimers involving the positions 4 as ring–ring bond sites, indicates that, also in the case of radicals **4a** and **4b**, the electron-spin density is far larger located on carbons 4.[3b] Nevertheless, notwithstanding the considerable steric hindrance about the carbons 2, electron-spin density on the said carbons is sufficiently large to allow the formation of substantial amounts of both 2,2′- and 2,4′-linked dimers.

The anaerobic photo-induced rearrangement of the dimers **6a**, **7a**, **8a** as well as of **6b**, **7b**, **8b** is consistent with a unimolecular homolysis process producing the radicals **4a** and **4b**, which rapidly recombine to form the photochemically stable dimers **5a** and **5b**. As evident from Figs. 3 and 4, the 2,2′-linked dimers undergo homolysis considerable faster than do 2,4′-linked dimers because of their greater steric crowding in the region of the bond undergoing cleavage. Similar photocatalysed rearrangements of NAD^+ and other nicotinamide dimers have been already reported.[1c,8] These simple isomerizations indicate that the carbon–carbon bond coupling the dihydropyridine moieties is so weak that only a low activation energy is required for the dimer's dissociation into pyridinyl radicals. Evidently, besides the steric factors, the resonance stabilization of the radicals being formed is the determining factor which allows a lower activation energy requirement for the homolysis. An unexpectedly low activation energy was also found for the thermal rearrangement of dimer **1** to **2**.[5]

Experimental

Materials and methods

Pyridine-3,5-dicarboxylic acid was purchased from Aldrich Chemical Co. All the other chemical reagents and solvents were purchased from Fluka Chemie A.G.

Melting points were taken on a Tottoli apparatus and are uncorrected. UV spectra were recorded on a Perkin-Elmer Lambda 40 UV/Vis spectrophotometer. The spectrophotometric data were processed using the Perkin-Elmer UV WinLab software. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AM-200 and AMX-500 spectrometers; chemical shifts are given in ppm (δ) from tetramethylsilane as internal standard; coupling constants (J) are in Hz.

Mass spectral data were obtained on a Waters 2 MD detector, using positive electrospray ionization mode (ESI +).

Analytical HPLC was carried out with an LC Perkin-Elmer series 200 apparatus, equipped with Perkin-Elmer 235 C diode array detector and Merck RP-18 LiChroCART 250–4 7 μm and Supelco Hypersyl 250–4 7 μm columns. The chromatographic data were processed using Perkin-Elmer Turbochrom and Turboscan softwares. Preparative HPLC was carried out with a LC Perkin-Elmer series 3 apparatus, equipped with an LC 55 UV detector and a Merck RP-18 LiChroCART 250–25 7 μm column.

Table 4 ^{1}H NMR chemical shifts (ppm) and coupling constants (Hz) of 2,4′-linked dimers[a]

							NCH_2 or $N'CH_2$										
	H_2	H_4	H_6	$H_{2'}$	$H_{4'}$	$H_{6'}$	H^a	H^b	H^a	H^b	NH	CH_3	NH_2	$J_{2,4}$	$J_{2',4'}$	$J_{4,6'}$	$J_{2'6'}$	JCH_3NH
6a	4.45 d	7.03 d	7.06 d	7.04 d	4.04 d	7.01	4.38 d $J_{a,b}$ 15.25	4.07 d	4.60 d $J_{a,b}$ 15.25	4.56d	6.17 d 6.26 d 7.60 d [a]	2.65 d 2.70 d 2.76 d 2.77 d		1.15	1.35	2.00		4.65 4.65 4.65 4.50
6b	4.41 d	7.18 s or 7.21 s		6.98 d	3.97 d	7.00 d	4.37 d $J_{a,b}$ 15.75	3.99 d	4.59 d $J_{a,b}$ 15.25	4.54 d			6.38 6.58		2.37		1.58	

[a] DMSO-d_6; in the spectra of compounds **6a** and **6b**, the aromatic proton signals are in the regions δ 7.22–7.50 and δ 7.25–7.43, respectively. [b] Signal obscured by the aromatic proton signals.

Controlled-potential electrolyses were performed by means of an Amel mod 555/A potentiostat equipped with an Amel mod 721 analogic integrator, and a three compartment cell, according to the procedure reported in a previous paper.[3a]

Photocatalysed isomerizations were carried out in vacuum-sealed vials using a shortwave (254 nm) Spectroline UV lamp, mod. EF-140C, one 4 W tube, peak intensity 570 μW cm^{-2} at 15 cm.

N,N′-Dimethyl pyridine-3,5-dicarboxamide

Pyridine-3,5-dicarbonyl dichloride (12 g) was added portion-wise to 100 cm^3 of stirred, ice-cooled 40% aq. methylamine. The precipitated solid was filtered off, and washed with cold water. Recrystallization from aq. EtOH gave pure *N,N′*-dimethyl pyridine-3,5-dicarboxamide (9 g, 62%); mp (from aq. EtOH) 220–222 °C (lit.,[9] 221–223 °C); δ_H (500 MHz; DMSO-d_6) 9.08 (2H, d, *J* 1.9, H2), 8.79 (2H, m, NH), 8.57 (1H, t, *J* 1.9, H4), 2.81 (6H, d, *J* 3.5, CH_3).

Pyridine-3,5-dicarboxamide

12 g of pyridine-3,5-dicarbonyl dichloride were added portion-wise to 150 cm^3 of stirred, ice-cooled 30% aq. ammonia. The precipitated solid was filtered off, and washed with cold water. Recrystallization from aq. EtOH gave pure pyridine 3,5-dicarboxamide (7.5 g, 77%); mp (from aq. EtOH) 303–305 °C (lit.,[9] 303–304 °C); δ_H (500 MHz; DMSO-d_6) 9.11 (2H, d, *J* 1.8, H2 + H6), 8.64 (1H, t, *J* 1.8, H4), 8.24 (2H, s, NH^a), 7.64 (2H, s, NH^b).

Pyridinium salts 3a and 3b

Benzyl bromide was added dropwise to an acetonitrile solution of the appropriate pyridine derivative. The solution was then heated under reflux for 16 h. On cooling, the separated solid was filtered off, and washed successively with cold acetonitrile and diethyl ether. Recrystallization from EtOH gave in good yield (85–90%) the expected pyridinium salt.

1-Benzyl-3,5-bis(methylcarbamoyl)pyridinium bromide 3a. Mp (from EtOH) 259–260 °C; δ_H (500 MHz; DMSO-d_6) 9.66 (2H, d, *J* 1.56, H2 + H6), 9.30 (1H, t, *J* 1.56, H4), 9.18 (2H, m, NH), 7.44–7.59 (5H, m, ArH), 5.96 (2H, s, CH_2), 2.87 (6H, d, *J* 4.62, CH_3).

1-Benzyl-3,5-dicarbamoylpyridinium bromide 3b. Mp > 300 °C; δ_H (500 MHz; DMSO-d_6) 9.67 (2H, d, *J* 1.60, H2 + H6), 9.38 (1H, d, H4), 8.60 (2H, s, NH^a), 8.23 (2H, s, NH^b), 7.45–7.63 (5H, m, ArH); 5.97 (2H, s, CH_2).

Electrochemical reduction of salt 3a

1-Benzyl-3,5-bis(methylcarbamoyl)pyridinium bromide **3a** (1.3 g) was added to 300 cm^3 of pH 7 0.1 M NaH_2PO_4 buffer and the solution was electrolysed at −1.0 V *vs* SCE, under vigorous stirring and in the dark. After 2 h a faradaic value of 1 ± 0.1 was measured, consistent with the uptake of one electron per mole of pyridinium salt, while the current intensity fell to the value of the pre-electrolysed buffer solution. The suspension was extracted with three 100 cm^3 portions of dichloromethane. The organic solution was washed with water, dried (Na_2SO_4), and then evaporated to yield 950 mg of a crude residue that was analysed by HPLC with the following solvent system: MeOH 42%–0.01 M aq. NH_4HCO_3 58%; flow rate 1 cm^3 min^{-1}. The eluate was monitored at 275 and 380 nm. The elution profile showed four peaks: I (t_R 46.5 min, λ_{max} 286 and 409 nm), II [t_R 52 min, λ_{max} 261 (sh) and 362 nm], III (t_R 54 min, λ_{max} 285 and 410 nm) and IV (t_R: 79.5 min, λ_{max} 295 and 390 nm) (Fig. 1a, b).

The following dimer relative abundance was shown by ^{1}H NMR spectroscopy performed on crude reduction mixture: **7a** (I) 6%; **5a** (II) 53%; **8a** (III) 5%; **6a** (IV) 36%.

Preparative HPLC (eluent MeOH 55%–0.07 M aq. NH_4HCO_3 45%; flow rate 8 cm^3 min^{-1}) of the crude residue (950 mg) gave three fractions. Each fraction was evaporated under vacuum to eliminate the methanol, the aqueous solution was repeatedly extracted with dichloromethane, and, lastly, the organic solvent was removed.

The first fraction afforded 1,1′-dibenzyl-1,1′,2,2′-tetrahydro-*N*,*N*′,*N*″,*N*′-tetramethyl[2,2′]bipyridinyl-3,3′,5,5′-tetracarboxamide **7a**; mp 164–166 °C; UV(MeOH) λ_{max} 286 and 409 nm; MS (ESI) *m*/*z* 591.2 (M + Na)$^+$; ^{13}C NMR (see Table 1), ^{1}H NMR (see Table 3).

1,1′-Dibenzyl-1,1′,4,4′-tetrahydro-*N*,*N*′,*N*″,*N*′-tetramethyl-[4,4′]bipyridinyl-3,3′,5,5′-tetracarboxamide **5a** (400 mg, 40% yield with respect to the salt **3a**) was obtained from the second fraction; mp (from AcOEt) 189–191 °C; UV(MeOH) λ_{max} 261 sh and 362 (ε 6990) nm; MS (ESI) *m*/*z* 591.2 (M + Na)$^+$; ^{13}C NMR (see Table 1), ^{1}H NMR (see Table 3).

The third fraction yielded 1,1′-dibenzyl-1,1′,2,4′-tetrahydro-*N*,*N*′,*N*″,*N*′-tetramethyl[2,4′]bipyridinyl-3,3′,5,5′-tetracarboxamide **6a** (270 mg, 27% yield with respect to the salt **3a**); mp (from AcOEt) 176 178 °C; UV (MeOH) λ_{max} 295 nm (ε 14 600) and 390 (ε 5336); MS (ESI) *m*/*z* 591.2 (M + Na)$^+$; ^{13}C NMR (see Table 2), ^{1}H NMR (see Table 4).

Electrochemical reduction of salt 3b

1-Benzyl-3,5-dicarbamoylpyridinium bromide **3b** (1.3 g) was added to 300 cm^3 of pH 7 0.1 M NaH_2PO_4 buffer, and the solution was electrolysed, in the dark, at −1.0V *vs* SCE under the above reported conditions. At the end of the electrolysis the solution was lyophilized, in a dark-glass flask, to a dry residue, which was extracted with MeOH. Removal of the solvent yielded a crude product (900 mg), which was analysed by HPLC using the following solvent system: MeOH 55%–0.01 M aq. NH_4HCO_3 45%; flow rate 1 cm^3 min^{-1}. The eluate was monitored at 275 and 380 nm.

The elution profile showed four peaks: I (t_R 6.5 min, λ_{max} 288 and 402 nm), II (t_R 9.2 min, λ_{max} 262 and 369 nm), III (t_R 10.3 min, λ_{max} 288 and 402 nm) and IV (t_R 11.5 min, λ_{max} 295 and 388 nm) (Fig. 3a, b).

The following dimer relative abundance was shown by ^{1}H NMR spectroscopy performed on the crude reduction mixture: **7b** (I) 4.5%; **5b** (II) 49%; **8b** (III) 6.5%; **6b** (IV) 40%.

Preparative HPLC (eluent MeOH 45%–0.07 M aq. NH_4HCO_3 55%; flow 7 cm^3 min^{-1}) of the crude residue (900 mg) gave two fractions. Each fraction was evaporated under vacuum to eliminate the methanol, the aqueous solution was repeatedly extracted with dichloromethane, and the organic solvent removed to dryness.

1,1′-Dibenzyl-1,1′,4,4′-tetrahydro-[4,4′]bipyridinyl-3,3′,5,5′-tetracarboxamide **5b** (350 mg, 35% yield with respect to the salt **3b**) was obtained from the first fraction, mp 194–196 °C; UV (MeOH) λ_{max} 262 (ε 13 950) and 369 nm (ε 7150); MS (ESI) *m*/*z* 534.8 (M + Na)$^+$; ^{13}C NMR (see Table 1), ^{1}H NMR (see Table 3).

The second fraction yielded 1,1′-dibenzyl-1,1′,2,4′-tetrahydro[2,4′]bipyridinyl-3,3′,5,5′-tetracarboxamide **6b** (250 mg, 25% yield with respect to the salt **3b**); mp 182 184 °C; UV (MeOH) λ_{max} 295 (ε 14 300) and 388 nm (ε 5250); MS (ESI) *m*/*z* 534.8 (M + Na)$^+$; ^{13}C NMR (see Table 2), ^{1}H NMR (see Table 4).

Photocatalysed rearrangement of 2,2′-and 2,4′-linked dimers to 4,4′-linked dimers

Samples of the crude mixtures from the reduction of **3a** and **3b** were dissolved in CH_2Cl_2 and exposed to irradiation, at 254 nm, in vacuum-sealed vials. At appropriate time intervals the composition of the solutions was monitored by analytical HPLC: the chromatograms showed the rapid disappearance of the 2,2′-linked dimers, the gradual decrease of the 2,4′-linked dimers, and the corresponding increase of the 4,4′-linked dimers (Figs. 2a, b; 4a, b). Dimers **7a**,**b** and **8a**,**b** totally disappeared in 10–15 min whereas the complete transformation of dimers **6a**,**b** into **5a**,**b** was observed after 160–180 min.

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