Structure of the Dimers Obtained From the Reduction of 1-Benzyl-3,5-bis(dialkylcarbamoyl)pyridinium Ions – Models of NAD$^+$

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In aqueous media the one-electron reduction of the title compounds on a mercury pool generally gives rise to three dimers, which are distinguishable by HPL chromatography. From spectroscopic analyses it has been possible to propose a structure for these conformers and their stability has been studied. Two conformers are unstable, yielding the third conformer. A mechanism is proposed for this transformation.

Several papers are devoted to the structural analysis of dimeric products obtained from the electrochemical reduction of 1-alkyl-3-carbamoylpyridinium, as NAD$^+$ models (Nicotinamide Adenine Dinucleotide, in the oxidized form), in aqueous media. Generally, the authors claim to have isolated dimers having the structure of the 1,1′,4,4′-tetrahydro-4,4′-bipyridine derivative[1]. Underwood[2][3], and more recently Carelli[4], have also proposed the formation of 6,6′ dimers. Although in most cases the electrochemical reduction of 1-substituted nicotinamide salts led to the formation of several dimers, the 4,4′ dimer was obtained as the major product, whilst a minor amount of the 4,6′ dimer was obtained, the rest being very small quantities (less than 5%) of 2,2′, 2,4′, and 6,6′ dimers. Some of these dimers isomerized into the 4,4′ dimer, showing that the bond between the two dihydropyridine rings is very weak and that the dimer is in equilibrium with its radical[5]. The same holds true for the biological NAD$^+$ since three diastereoisomers with the 4,4′ structure were detected by Carelli[6] and six diastereoisomers by Jaegfeld[7]. These results are explained by the asymmetrical environment of the two carbon atoms involved in the bond between the two rings. Moreover, Carelli et al. showed that the ring carbon reactivity follows the position order 4 > 6 > 2 for 3-monosubstituted nicotinamide salts[4], due to the electron-withdrawing effect of the carbamoyl substituent grafted onto the ring. Thus, one can suggest that for 3,5-disubstituted pyridinium salts the electrochemical dimerisation should lead to the formation of the 4,4′ dimer only which, because of the symmetry of the molecule, could not give rise to diastereoisomers (in contrast to monosubstituted salts). So, when we studied the dimeric product obtained during the electrochemical reduction of the title compound (see Scheme 1) we were surprised to observe the formation of three dimers in nearly equal amounts in most cases. The first idea was that regioisomers were obtained, but as carbon atoms 2 and 6 are less reactive than carbon atom 4, in addition to the 4,4′ dimer the 2,4′ or 2,6′ possible dimers should have only been obtained as traces. So we developed a research strategy to look at the structure of the different dimeric species obtained from a one-electron reduction of symmetrical 3,5-disubstituted pyridinium ions, taken as an NAD$^+$ model.

We chose to study the 1-benzyl derivative whose dimers are obtained by a one-electron reduction on a mercury pool, well separated on an analytical HPL chromatogram and easily analysed by NMR. Although in this paper we give the results obtained for two 3,5-dicarbamoylpyridinium cations (**I**, **II**), the properties are similar to those observed for 3,5-disubstituted pyridinium salts described previously[8][9].

At the end of this work, some brief results are given on the 1,3-bis[3,5-bis(*N*-methylcarbamido)pyridinio]propane (**III**), a bis-pyridinium salt studied in order to corroborate our assumptions on the formation of conformational dimers (see Scheme 1).

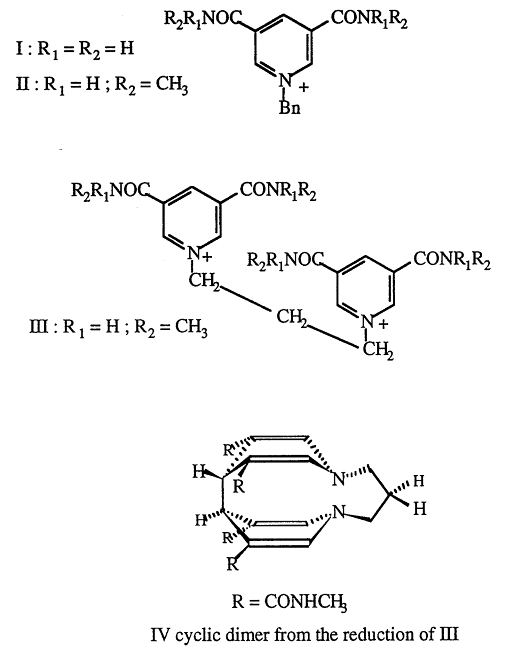
Results and Discussions

Monoelectronic Reduction

It has been shown that all the 3,5-dicarbamoyl-substituted pyridinium salts behave like NAD$^+$ itself; they are reducible on a dropping mercury electrode in two steps by two successive one-electron transfers at -0.65 ± 0.03 V and -1.4 ± 0.1 V[8][9]. These values depend very slightly on the substituents grafted onto the nitrogen atom of the ring, and on the nitrogen atoms of the two amidic groups. The electrolysis of a millimolar solution of **I** on a mercury pool electrode at -1.1 V in an aqueous buffered medium (pH =

1434−193X/98/1010−2237 $ 17.50+.50/0

Scheme 1. Structure of the studied compounds



7) consumes one electron per molecule and leads to a yellow solution. Successive spectrophotometric UV/Vis spectra recorded during the electrolysis show the appearance of two bands at 377 and 279 nm and three isosbestic points at 261, 242, and 212 nm (Figure 1), whereas in the same time period three well-behaved peaks **A**, **B**, and **C** appear on the chromatogram, increasing in intensity with the progress of the reaction (see Figure 2a). As previously observed, the relative concentrations of **A**, **B**, and **C** depend on several factors, such as the pyridinium salt itself, the temperature or the electrode material[8]. It is probable that adsorption phenomena of the pyridinium ion on the electrode play a major role[9]. The formation of these three compounds is also observed when the reduction is carried out chemically using magnesium powder, but in this case, since the reaction takes place in a heterogeneous medium, the adsorption reaction may also be invoked. On the other hand, studies of the coproportionation of dihydropyridine and pyridinium salts show, under homogeneous conditions and in the dark, the formation of only one stable dimer[9].

The electrolyzed solution is stable for many days when kept in darkness at room temp. under nitrogen, or for several hours even at 50°C as shown by chromatography. This stability is much higher than that quoted for the positional 4,6′ dimer of other 3-monosubstituted pyridinium salts, where rearrangements occur with the formation of positional isomers either at room temp. or by heating the mixture[5]. On the other hand, the exposure of the solution in a quartz cell to the light of a xenon lamp leads to the disappearance of two chromatographic peaks while the third one increases (see Figure 2b). When the detection wavelength of the apparatus is fixed at a value corresponding to an isosbestic point (λ = 242 nm) in order to obtain peak areas proportional to the concentration of the various dimers, we observed a quantitative transformation of the two dimers into the third dimer without any formation of by-products. This result does not agree with the postulate of a ring-ring junction homolysis, which is usually controlled by a thermal process[13]. Moreover, the absence of the formation of a dihydropyridine and/or pyridinium salt which would result

Figure 1. UV/Vis spectra obtained during the electrochemical reduction on mercury drop of **I** (1.6 mM) in aqueous medium containing 0.1 M PO_4^{3-}-buffered at pH = 7 (*l* = 1 mm); *Q* (F) = 0 (**1**), 0.1 (**2**), 0.25 (**3**), 0.42 (**4**), 0.6 (**5**), 0.80 (**6**), 0.92 (**7**), 1.05 (**8**)

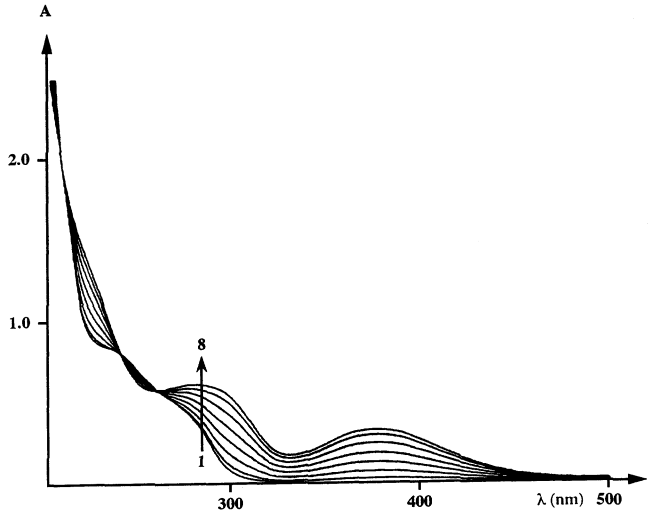
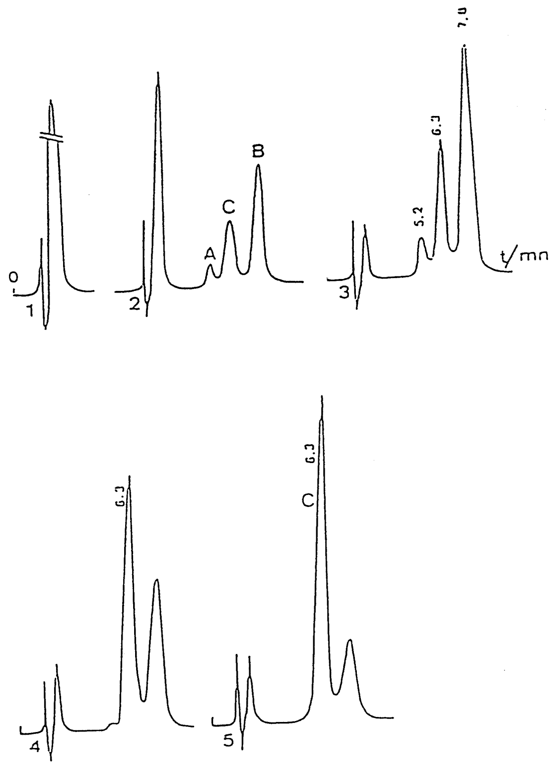


Figure 2. HPL chromatography of $1.2 \cdot 10^{-3}$ mol dm^{-3} of **I** during an electrolysis (**1**, **2**, **3**) and then exposure to the light (**4**, **5**): (a) quantity of electricity (F/mol): 0 (**1**), 0.5 (**2**), 1 (**3**); (b) time of irradiation of the solution of **3** in min: 41 (**4**), 98 (**5**); column C18, eluent: ethanol/water (30:70) + $5 \cdot 10^{-2}$ mol dm^{-3} NaH_2PO_4, pH = 7, flow rate: 2 ml min^{-1}



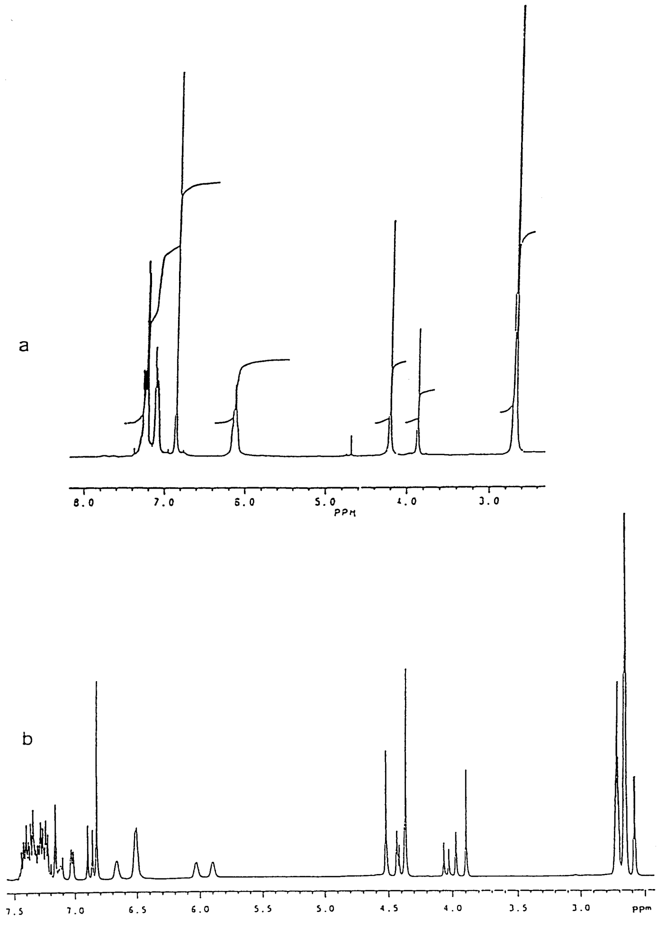
from the reaction between water (the medium of the experiments) and the radical species allows us to confirm that an homolysis step did not take place during the transformation process. Therefore a more detailed study of this transformation was undertaken.

The mass spectrum of the yellow powder extracted from the solution confirms the presence of dimeric compounds. Its chromatogram presents the same three peaks as seen previously in the ratio 70:20:10. We will see later that one of these three dimers is stable and easily isolable and has a mass spectrum showing the same fragmentation peaks as the mixture. That is the first indication of the formation of stereoisomers.

Structure of the Stable Dimer

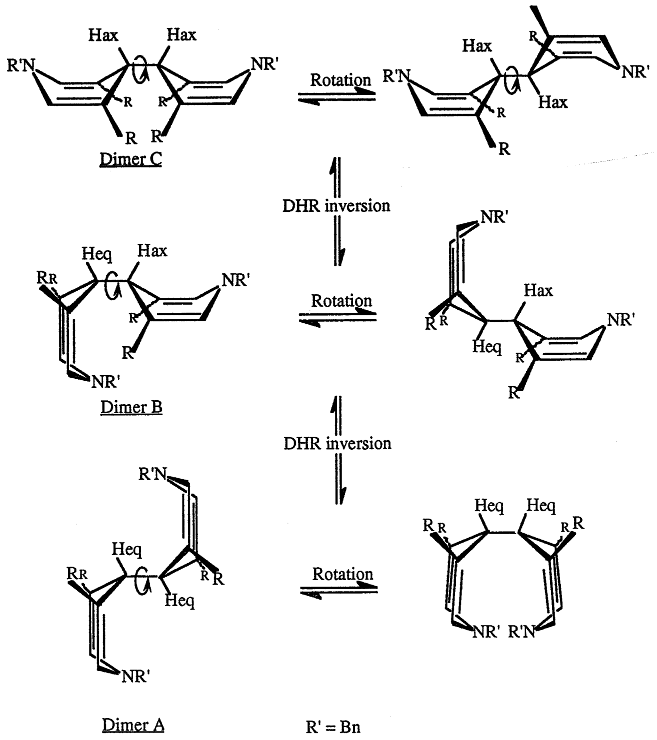
In order to determine the structure of the stable dimer we chose to study the dimer obtained from the pyridinum salt **II** after exposure to the light of a xenon lamp. The methyl groups of this salt make the interpretation of the NMR spectra easier. The stable dimer of **II** is extracted and analyzed by ^{1}H (see Figure 3a) and ^{13}C NMR.

Figure 3. (a) ^{1}H-NMR (200 MHz) spectrum in CD_3CN of the stable dimer obtained from **II**; (b) ^{1}H-NMR (400 MHz) spectrum in CD_3CN of dimers obtained from **II**; $\delta = 2.58$ (compound **A**) 2.73 and 2.71 (asymmetrical compound **B**)



Whereas mass spectrometry confirms that it is a dimer, the two NMR spectra are in a good agreement with a symmetrical product, since the two pyridinic rings are equivalent. One can assume that this compound is a symmetrical 4,4′ dimer. X-ray structure analyses of dihydropyridines show that in fact the heterocyle has a flattened boat conformation[14][15][16][17]18]. Many authors studying 4-aryl-1,4-dihydropyridines have pointed out that the hindered substituent may occupy a pseudoaxial and/or a pseudoequatorial position. Interconversion between the two forms is possible by inversion of the heterocycle[19][20] (see Figure 4).

Figure 4. Structures proposed for the conformational isomers



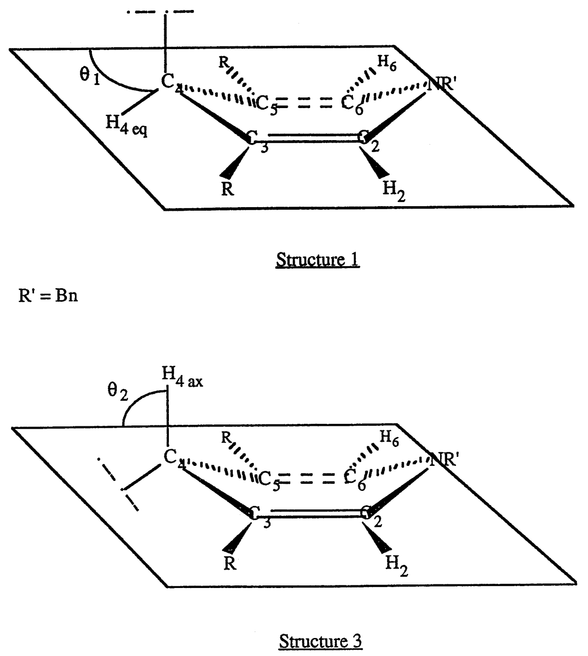
An NMR analysis of the three possible structures gives the following information for the theoretical coupling constants H−C and H−H, and Figure 4 represents the various dihedral angles involved in the analysis. The plan drawn contains the 4 carbon atoms C^2, C^3, C^5, C^6 of the dihydropyridine ring of the dimer. From X-ray structures of some 1,4-dihydropyridines it is possible to have an idea of the particular dihedral angles expected for these dimers. The comparison of the theoretical coupling constants[21] with those measured by NMR spectroscopy allows identification of the structure of the stable dimer.

Structure **1**: Dihedral angle C^4H^4/C^2H^2: $\theta_1 \approx 0°$, J[theo(H^2-H^4)] = 2 Hz[21]; C^4H^4/C^2C^3: $\theta_1 \approx 0°$, J[theo(H^4-C^2)] = 10−12 Hz.

Structure **2**: The two heterocycles are not equivalent. This structure is not in agreement with the NMR spectrum of the stable dimer **C** since, if this were the case, each signal should be divided into two others.

Structure **3**: Dihedral angle C^4H^4/C^2H^2: $\theta_2 \approx 90°$, J[theo(H^2-H^4)] = 0 Hz[21]; C^4H^4/C^2C^3: $\theta_2 \approx 90°$; J[theo(H^4-C^2)] = 4−6 Hz.

Figure 5. Dihedral angle between the coupled atoms (half part of the symmetrical dimers)



A careful analysis of the NMR spectra of the stable dimer shows that the resonance signals of both H^2 and H^4 are composed of a single narrow peak with a width of less than 1 Hz. On the other hand, the value of the coupling constant $J[H^4-C^2]$ is 5 Hz. Thus, the structure **3** is proposed for the stable dimer **C** (see Figure 5). Since the 1,4-dihydropyridine compounds do not show the same behaviour, this means that, due to the low energy required for the nitrogen inversion, the benzyl group is in the preferential equatorial position.

Structure of the Unstable Dimers

The NMR spectra were recorded in deuteriated acetonitrile (CD_3CN) of a freshly extracted mixture of dimers. The spectra always showed the presence of one major product (70%), the stable dimer, and of two less abundant unstable dimers (20% and 10%). The analysis of the methyl resonance peaks shows that the three isomers are present in relative concentrations comparable to those measured by chromatography. Figure 3b represents the NMR spectrum of the mixture of the dimers in CD_3CN; for each particular hydrogen atom one can observe a large signal, attributed to the stable dimer, surrounded by two small signals, attributed to the unstable dimers. Only these small signals will be studied hereafter. If the 2,2′ and 2,4′ isomers were the unstable dimers, as formerly quoted by Ohnishi[5] for some monosubstituted pyridinium salts, the following ^{1}H-NMR resonance spectrum should be observed (see Scheme 2 and Table 1).

Scheme 2. Structure of the possible dimers

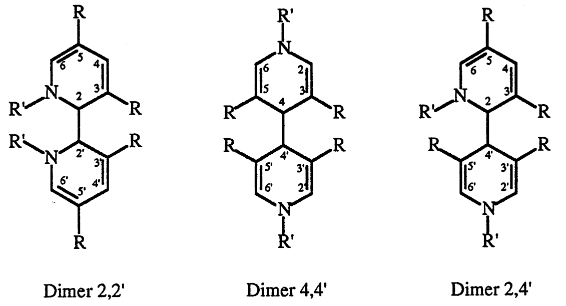


Table 1. Number of ^{1}H-NMR peaks (N) expected for 2,4′ and 2,2′ isomers of **II**; comparison with the observed spectrum

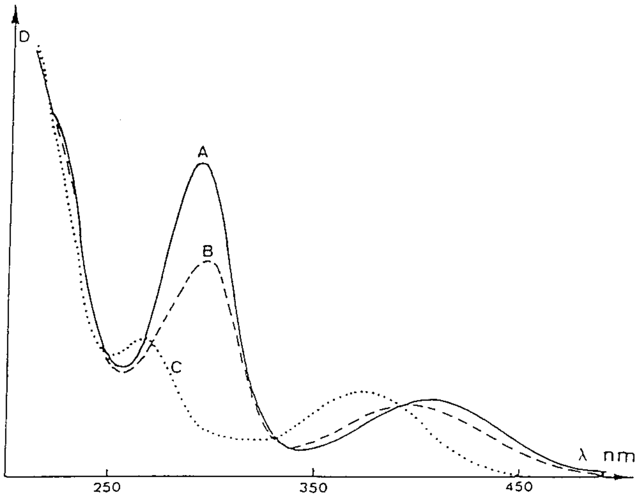
H groups	N (theoretical) 2,4′ dimer	2,2′ dimer[d]	N (observed)
CH_3	3 or 4[a] × 2[b]	2 × 2[d]	4 + 2
	6 or 8	4	
H−C−C	H^4, H^6: 2	H^4, H^6, $H^{2'}$, H^6	
	$H^{2'}$, H^6: 1 or 2[c]	2 × 2[d]	2 + 1
	3 or 4	4	
H−C	H^2	$R^2,R^{2'}$ and $S^2S^{2'}$	
	coupled 2 × 2 = 4	H^2, $H^{2'}$: 2 × 2[d][e]	[f]
	$H^{4'}$	*meso*: H^2, $H^{2'}$: 1	
		5	
CH_2 (Bn)		1 × 2[d]	2 + 1
	2	2	

[a] The environments of CH_3 in 3′ and 5′ could be slightly different. – [b] The methyl groups are coupled with the vicinal amidic proton. – [c] The environments of $H^{2'}$ and $H^{6'}$ are slightly different. – [d] The dimerization in the positions 2,2′ induces the formation of enantiomers: $R^2R^{2'}$, $S^2S^{2'}$, *meso*. – [e] H^2, $H^{2'}$ are coupled. – [f] Hidden under the aromatic H signals.

There is no agreement between the number of NMR peaks expected in the case of the formation of 2,2′ and 2,4′ isomers and the actual number of peaks observed in Figure 2b. In addition, a more careful analysis of the spectrum shows that one of the two small signals always has twice the number of peaks as the other. For example the resonance of the methyl group of the dimer of **II** appears in CD_3CN as one doublet at $\delta = 2.58$ (coupling with the vicinal H atom signal of the amidic NH at $\delta = 6.52$) and two doublets at $\delta = 2.71$ and 2.73 (coupled with amidic NH signal situated at $\delta = 6.02$ and 5.90, respectively). The same holds true for the other hydrogen atoms. This observation is in accordance with the formation of one symmetrical and one asymmetrical dimer[13]. The postulate of positional isomers is not in agreement with the NMR spectra, therefore another structure for these unstable dimers has to be proposed. Goldmann et al.[20], have proposed three structures of this 4,4′ dimer, differing from each other by conversion of one chair form to the other, since the dihydropyridine heterocycle is not planar. Thus, one can invoke the idea that our dimers form the same conformational equilibria and in this case, three conformations are possible, as shown in Figure 4.

We may have an idea of the conformation of the most unstable dimer and we will see below that the two unstable dimers do not show the same kinetics when the electrolysis solution is exposed to the light. The UV/Vis spectrum of each was recorded using a chromatograph equipped with a diode array detector (Figure 6). The comparison of these spectra shows that the most unstable dimer has the largest extinction coefficient for the absorption band around 300 nm. The increase of this absorption with the instability of this dimer could be due to a higher interaction between the two heterocycles. Only the structure **1**, in which the two rings are in axial (less favoured) position, allows a maximum interaction between the two heterocycles (Figure 4). Thus, the structure **1**, which is symmetrical, leads to a simple NMR spectrum, whereas the asymmetrical structure **2** requires each signal to be split into two, as stated before.

Figure 6. UV/Vis spectrum of the three dimers (arbitrary units); λ_{max} (nm) = 404, 292 (dimer **A**); 397, 295 (dimer **B**); 370, 266 (dimer **C**)



Kinetics of the Reaction A + B → C

When a freshly electrolyzed solution containing a mixture of the three dimers is exposed to the light of a xenon lamp, the absorption at 242 nm (one of the isosbestic points mentioned above) did not vary, whereas two chromatographic peaks vanished and the third one increased. In order to have reproducible conditions of measurement, the quartz cell was exposed to the light at a constant distance from the source (see Experimental Section). It was observed that the rate of loss of the two unstable dimers did not show the same kinetics but that both are first-order kinetic reactions. Two mechanisms are possible for this transformation.

$$\alpha \begin{cases} A \xrightarrow{k_1} C \\ B \xrightarrow{k_2} C \end{cases}$$

$$\beta \quad A \xrightarrow{k_1} B \xrightarrow{k_2} C$$

where k_1 and k_2 are the kinetic constants of the two reactions. The expression of the concentration of the three species versus time is easy to calculate for both proposed mechanisms **α** and **β**.

$$\alpha: \quad [A] = [A]_0 \exp(-k_1 t) \qquad (1)$$

$$[B] = [B]_0 \exp(-k_2 t) \qquad (2)$$

$$[C] = [C]_0 + [A]_0 \exp(1 - k_1 t) + [B]_0 \exp(1 - k_2 t) \qquad (3)$$

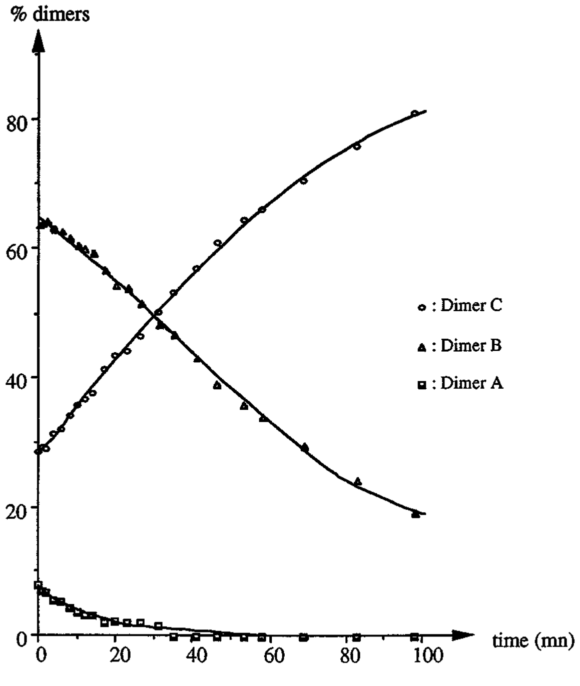
$$\beta: \quad [A] = [A]_0 \exp(-k_1 t) \qquad (4)$$

$$[B] = \frac{k_1}{k_2 - k_1}([A]_0 \exp(-k_1 t) + ((k_2 - k_1)[B]_0 - k_1[A]_0) \exp(-k_2 t) \qquad (5)$$

$$[C] = [A]_0 + [B]_0 + [C]_0 - [A] - [B] \qquad (6)$$

$[\mathbf{A}]_0$, $[\mathbf{B}]_0$, and $[\mathbf{C}]_0$ are the initial concentrations of the three dimers. The reaction is followed by chromatography, and [**A**], [**B**], [**C**] are determined by the measurement of the peak areas, which are proportional to the concentration of the dimers [$\lambda = \lambda$(isosbestic point)]. K_1 is calculated from the evolution of **A** at the beginning of the reaction, since **A** is the most unstable entity, and k_2 from the evolution of **B** at the end of the reaction when **A** has disappeared (see Figure 7). The values found for k_1 and k_2 are then introduced into the equations (1−3) or (4−6). An agreement between the theoretical evolution of the concentrations of the dimers versus time with the experimental values was observed only in the case of the mechanism **β** (see Figure 7).

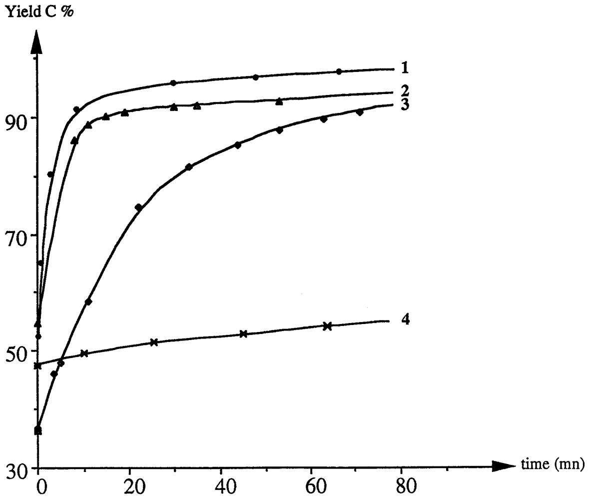
Figure 7. Evolution of the relative concentration of the three dimers of **I** during the exposure to the light of a xenon lamp; solid lines: theoretical calculations for the mechanism **β**



The k_1 and k_2 values depend on many parameters: i.e source of light, power of the source, distance from lamp to cell etc. We give a value found when an experiment was carried out in a thermostated cylindrical quartz cell (length: 5 cm; diameter: 1 cm; θ: 18°C) placed at a distance of 50 cm from the xenon lamp. We found $k_1 = 8.5 \cdot 10^{-2}$ min^{-1} and $k_2 = 1.35 \cdot 10^{-2}$ min^{-1} ($k_1/k_2 = 6.3$).

The experiments, when repeated several times, show that k_1 and k_2 also depend on the range of the excitation wavelength (the most effective range covers the yellow absorption band) and on the alkylamidic substituents; the more hindered the substituent, the slower is the isomerization reaction of the dimer (see Figure 8).

Figure 8. Influence of the amidic substitution on the kinetics of the transformation of the dimer **B** into the (stable) dimer **C**. − **1**; $R_1 = R_2 = H$; **2**: $R_1 = H$, $R_2 = Me$; **3**: $R_1 = H$, $R_2 = Et$; **4**: $R_1 = R_2 = Et$



Behaviour of the Bis-pyridinium Salt III

We cannot ignore that another possible reason for the existence of these isomers could be attributed to the inversion of the amidic nitrogen atoms. For this reason, we have studied the behaviour of the bis-pyridinium salt **III** in which the two pyridinium rings are separated by three methylene groups. Deronzier et al.[22] have shown, in the case of the electrochemical study of bis-dipyridinium salts, that the stronger interaction between the two one-electron-reduced bis-pyridinium salts is observed when the two heterocycles are separated by a propyl chain. Since the high tension of this reduced molecule does not allow the inversion of the heterocycle a unique cyclic dimer is expected from the reduction of this compound. The polarogram of this compound in an aqueous medium exhibits only one wave with $E_{1/2} = -0.38$ V relative to two simultaneous electron transfers, and the 30 mV slope found for the logarithmic transform $dE/d \log[I/(I_{\text{limit}} - I)]$ allows us to confirm the two reversible electron tranfers. Thus, the strong interaction between the two radical moities generated allows to favour a rapid cyclisation due to the internal coupling reaction of the biradical species. The yellow product isolated from macroscale electrolysis contains only one compound (a unique chromatographic peak is observed) although many eluents were tested. The reduced product has the same molecular weight as the initial compound (deduced from mass spectrometry). It is symmetric and cyclic, as observed by NMR, and therefore has the only envisageable structure including a 4,4′ bond (see Scheme 1). These results are in accordance with the fact that the cyclic dimer from **III** can take a unique conformation since the chair-chair conversion of the heterocycles is impossible. Moreover, the strong interaction between the two heterocycles leads to a UV/Vis spectrum that is very close to that obtained for the less stable dimer **A** for which the stronger interaction between the two rings can be observed. This result confirms our assumption concerning the presence of conformational dimers.

Conclusion

The electrochemical reduction of 3,5-disubstituted pyridinium salts lead to the formation of dimers which could be converted to a 4,4′ dimer. Whereas in the case of monosubstituted pyridinium salts authors claim the formation of positional isomers, we propose that for the symmetrical NAD^+ models studied, electrochemical reductions lead to a mixture of conformational dimers which can be converted into the 4,4′ dimer by chair-chair inversion of the dihydropyridine rings. This inversion is obtained by irradiation of the dimer mixture obtained by electrolysis. Kinetic aspects have been investigated and show that the inversion depends on the steric hindrance of the amidic groups in the 3,5 position and on the irradiation wavelength.

Experimental Section

Apparatus: The electrochemical apparatus has been formerly described in ref.[8]. All the potentials were referred to the SCE. − ^1H- and ^{13}C-NMR spectra: Brucker AC 200 or AM 400. − UV/Vis spectra: Cary 13 apparatus. − Fast atom bombardment (FAB) mass spectra: AIE Kratos MS 50 mass spectrometer fitted with an Ion Tech Ltd gun at the mass spectrometry service UJF-CNRS, CERMAV, Grenoble. A standard FAB source was used, and *m*-nitrobenzylalcohol (NBA) was the liquid matrix. − HPL chromatography: Waters apparatus equipped with a standard UV/Vis detector or with a photodiode array detector (Waters 990). The conditions of chromatography on a C18 column (250 mm lentgh × 4.6 mm diameter) are gathered in Table 2. The retention times were assigned from measurements with an authentic sample of the mixture of the three dimers obtained by chemical reduction of the pyridinium salt with magnesium in aqueous medium[10]. Retention times obtained with dihydropyridine derivatives[11][12] were added in order to show that no confusion was possible between dimers and dihydropyridine species. In all cases, the eluent also contained $5 \cdot 10^{-2}$ mol dm^{-3} NaH_2PO_4 and the pH was adjusted to 7 with NaOH (see Table 2).

Table 2. Conditions of chromatography: eluents and retention times (flow rate: 2 ml min^{-1})

Compound	Eluent % (v/v)	Retention time [min] Pyridinium	Dimers	Dihydropyridine
I	ethanol/water 30:70	3.3	5.2; 6.3; 7.8	3
II	ethanol/water 40:60	2.8	6.3; 7; 7.3	3.7
III	methanol/water 30:70	3	25	

Synthesis: The syntheses of **I** and **II** are described in ref.[8]. The bis-pyridinium salt **III** was obtained as follows: 1 g ($5.2 \cdot 10^{-3}$ mol) of 3,5-bis(*N*-methylcarbamido)pyridine was added to an excess of 1-chloro-2,4-dinitrobenzene (16 g, $7.9 \cdot 10^{-2}$ mol). The mixture was heated for 30 d at 70°C under nitrogen in a flask equipped with a reflux condenser. After cooling, the addition of 50 ml of methanol yielded the insoluble 1-(2,4-dinitrophenyl)-3,5-bis(*N*-methylcarbamido)pyridinium chloride which was filtered and washed with diethyl ether (yield 80%). 1 g (2.5×10^{-3} mol) of this product and 0.093 g ($1.25 \cdot 10^{-3}$ mol) of 1,3-diaminopropane (Fluka) were added to 50 ml of methanol. The mixture was refluxed for 12 h and then cooled before the addition of 200 ml of diethyl ether. The precipitate of **III** was isolated by filtration and washed with methanol (yield 95%).

Extraction of the Dimers: The electrolyses were carried out in 20 ml of buffered aqueous solution (pH = 7) containing 1 mol dm^{-3} of sodium phosphate salt on a mercury pool (15 cm^2) and 0.01 mol dm^{-3} of pyridinium salt. The yellow product, which precipitated during the electrolysis, was isolated after washing with water and drying under reduced pressure. − MS (FAB+) for dimer from **II**; *m/z*: 569 [M + 1], 538 [M − 2 CH_3], 507 [M − 4 CH_3], 284 [M/2]; (FAB−); *m/z*: 567 [M − 1].

The cyclic product obtained from the reduction of **III** was extracted in darkness as follows: the aqueous solution of electrolysis was concentrated under reduced pressure to dryness. Then, 25 ml of absolute ethanol was added and the solution filtered in order to eliminate the sodium salt. The filtrate was concentrated and the yellow product was purified by TLC (cellulose F, Merck) using a mixture acetonitrile/acetone (70:30, v/v) containing 0.1 mol dm^{-3} of $LiClO_4$ as eluent. MS of the cyclic product of **III** (FAB+); *m/z*: 429 [M + 1]; (FAB−); *m/z*: 427 [M − 1]. − ^1H NMR (D_2O, TMS): *endo/exo*: $\delta = 7.2, 7.5$ (s, $H^2 + H^{6'}$, $H^{2'} + H^6$, 4 H, $J_{2,6'} = J_{2,'6} = 1.17$ Hz), 5.4 (s, $H^4 + H^{4'}$, 2 H), 2.97 (s, CH_3, 3 H), 4.15, 3.6, 2.35 [m, 3 CH_2 (*endo/exo*), 6 H].

Irradiation Experiments: The irradiation experiments have been performed under inert atmosphere using a xenon lamp (OSRAM XBO, 250 W) in a thermostated quatz cell (lenght: 5 cm; diameter: 1 cm; θ: 18°C) placed at a distance of 50 cm from the xenon lamp.

[1] H. Baumgärtel, J. K. Retklav, *Encyclopedia of Electrochemistry of The Elements XV* (Eds.: A. J. Bard, H. Lund), M. Dekker, New York, **1984**, p 216.
[2] J. N. Burnett, A. L. Underwood, *J Org Chem.* **1965**, *30*, 1154.
[3] R. W. Burnett, A. L. Underwood, *Biochemistry* **1968**, *7*, 3328.
[4] V. Carelli, F. Liberatore, A. Casini, B. Di-Rienzo, S. Tortorella, L. Scipione, *New J. Chem.* **1996**, *20*, 125.
[5] Y. Ohnishi, M. Kitami, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2674.
[6] V. Carelli, F. Liberatore, A. Casini, R. Mondelli, A. Arnone, I. Carelli, G. Rotilio, I. Malvelli, *Bioorg. Chem.* **1980**, *9*, 342.
[7] H. Jaegfeldt, *Bioelectrochem. Bioenerg.* **1981**, *8*, 355.
[8] J. C. Leprêtre, D. Limosin, G. Pierre, P. Chautemps, G. Gellon, J. L. Pierre, *J. Electroanal. Chem.* **1990**, *286*, 63.
[9] J. C. Leprêtre, D. Limosin, G. Pierre, *J. Electroanal. Chem.* **1992**, *324*, 115.
[10] F.M. Moracci, F. Liberatore, V. Carelli, A. Arnone, I. Carelli, M. E. Cardinali, *J. Org. Chem.* **1978**, *43*, 3240.
[11] E. C. Loresey, W. C. Ross, *J. Chem. Soc. B* **1969**, 192.
[12] Z. Biellmann, H. J. Callot, *Bull. Soc. Chim. Fr.* **1968**, 115.
[13] F. T. McNamara, J. W. Nieft, J. F. Ambrose, E. S. Huyser, *J. Org. Chem.* **1977**, *42*, 988
[14] R. Fossheim, *J. Med. Chem.* **1986**, *29*, 305.
[15] J. E. Arrowsmith, S. F. Campbell, P. E. Cross, J. K. Stubbs, R. A. Burges, D. G. Gardiner, J. K. Blackburn, *J. Med. Chem.* **1986**, *29*, 1696.
[16] K. Tamazawa, H. Arima, T. Kojima, Y. Isomura, M. Okada, S. Fujita, T. Furuya, T. Takenaka, O. Inagaki, M. Terai, *J. Med. Chem.* **1986**, *29*, 2504.
[17] R. Davis, J. R. Kern, L. Kurz, J. R. Pfister, *J. Am. Chem. Soc.* **1988**, *110*, 7873.
[18] S. Goldmann, L. Born, S. Kazda, B. Pittel, M. Schramm, *J. Med. Chem.* **1990**, *33*, 1413.
[19] J. J. Baldwin, D. A. Claremon, P. K. Lumma, D. E. McClure, S. A. Rosenthal, R. J. Winquist, E. P. Faison, G. J. Kaczorowski, M. J. Trumble, G. M. Smith, *J. Med. Chem.* **1987**, *30*, 690.
[20] S. Goldmann, M. Stoltefuss, *Angew. Chem. Int. Ed. Eng.* **1991**, *30*, 1559.
[21] P. E. Hansen, *Prog. NMR Spectroscopy* **1981**, *14*, 175.
[22] A. Deronzier, B. Galland, M. Vieira, *Nouv. J. Chim.* **1982**, *6*, 97.

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