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Axel Bossavit, Valérie Monnier, Didier Siri, Gabriel Canard, Didier Gigmes, et al.. Controlled Reactivity of Viologens in Alkaline Solutions Via Cucurbit[7]uril Complexation. *European Journal of Organic Chemistry*, 2024, 27 (31), pp.e202400404. 10.1002/ejoc.202400404 . hal-04733006

**HAL Id: hal-04733006**

**<https://hal.science/hal-04733006v1>**

Submitted on 11 Oct 2024

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# Controlled Reactivity of Viologens in Alkaline Solutions Via Cucurbit[7]uril Complexation

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A series of *N*-alkyl- and *N*-aryl-viologens has been studied in alkaline solutions. In this work, we evaluated the deuteration rate of the viologens in D<sub>2</sub>O solutions of pH values ranging from 7.3 to 12.7. Kinetic experiments and computational calculations showed the high reactivity of H–C(2) bonds toward deprotonation of *N*-aryl-pyridinium moieties compared to *N*-alkyl-pyridinium moieties, even in hybrid *N*-aryl/*N*-alkyl dissymmetric viologens. However this high H–C(2) reactivity in liquid

phase contrasted with the proton fragmentation mechanism observed in the gas phase by mass spectrometry. The H/D exchange rate of viologens in very strong alkaline conditions could be significantly reduced using cucurbit[7]uril (CB[7]) as supramolecular protecting group. Ultimately, CB[7] inclusion led to a selective protection of H–C(2) group of *N*-aryl-pyridinium of dissymmetric viologens, and induced a supramolecular regioselective deuteration.

## Introduction

Dicationic 1,1'-difunctionalized-4,4'-bipyridinium salts (Scheme 1), also known as viologens, are versatile compounds that have been used in various research fields from biology<sup>[1]</sup> to materials science<sup>[2]</sup> but also for energy storage<sup>[3]</sup> and in molecular machines.<sup>[4]</sup>

Many disciplines are therefore increasingly producing and using these salts, raising the question of the stability and toxicity of viologen derivatives over time, and of their degradation.<sup>[5]</sup> The degradation of viologens is therefore an important issue and various processes, exploiting photo-redox methods, have been assessed.<sup>[6]</sup> Results have brought to light the low stability of viologen derivatives in strong alkaline solutions, leading to oxidation of the pyridinium core into pyridones<sup>[5d,7]</sup> via hydroxyl radical addition<sup>[8]</sup> or by a pseudobase resulting from the addition of a OH<sup>−</sup> (or OD<sup>−</sup>) on the viologen.<sup>[9]</sup> The dealkylation of dimethyl-viologen in strong alkaline solutions has also been hypothesized,<sup>[10]</sup> leading to the liberation of methanol potentially behaving as reductant and so accelerating its degradation.<sup>[9]</sup>

Recently, Zhang et al. reported a strategy to accelerate the degradation of alkylviologens in water based on formation of microdroplets, which enhanced electron exchange at the air–water interface to favor the viologen degradation with O<sub>2</sub>.<sup>[11]</sup> Beside free (or accessible) viologens, the authors evaluated the reactivity of viologens encapsulated in a macrocycle cavity, that of cucurbit[7]uril (CB[7], Scheme 1).<sup>[11]</sup> Actually, the host\*guest chemistry of cucurbit[*n*]uril (CB[*n*]) macrocycles and viologen is well known,<sup>[12]</sup> and allowed to build a large family of supramolecular complexes featured by a wide diversity of assemblies.<sup>[13]</sup> In particular, CB[7] complexes of viologen derivatives are consistently featured by quite high (1:1) binding constants *K*<sub>a</sub> of around 10<sup>5</sup>–10<sup>7</sup> M<sup>−1</sup> in water, due to the release of high energy water molecules from the hydrophobic cavity of CB[7],<sup>[14]</sup> and strong favorable dipole–cation interactions of the host carbonyl rims toward ammonium groups.<sup>[15]</sup> By shielding the bipyridinium skeleton of methyl-viologen from its environment, the CB[7] complexation, while weakly impacting the guest reduction potential,<sup>[16]</sup> dramatically limits its reactivity, leading to a toxicity decrease<sup>[17]</sup> and a stronger viologen stability.<sup>[11]</sup> In this context, NMR studies of viologens in D<sub>2</sub>O solutions showed a spontaneous deuteration of the H–C(2) groups (H<sub>a</sub> and H<sub>b</sub> protons in Scheme 1), a priori pointing to a quite unusual reactivity on aromatic groups.<sup>[18]</sup> In fact, the H/D exchange on carbon centers of heterocycles is almost thermo-neutral and has been largely reported in the literature.<sup>[19]</sup> While the H/D exchange can be controlled by a catalyst,<sup>[20]</sup> this reaction is also spontaneous in protic deuterated solvents such as D<sub>2</sub>O or methanol-D<sub>4</sub>.<sup>[21]</sup> Indeed the determination of H/D exchange rate constants is an elegant way to assess the reactivity of organic groups and this method has been used to investigate the H/D exchange on several aromatic molecules, CB[7] consistently decreasing the H/D exchange on specific sites of included molecules<sup>[22]</sup> albeit not with viologens.<sup>[23]</sup> Therefore, the impact of viologen derivatization on H/D rate exchanges and of CB[7] complexation, either central (on the bipyridinium core) or peripheral (on side-chains) had not been studied to the

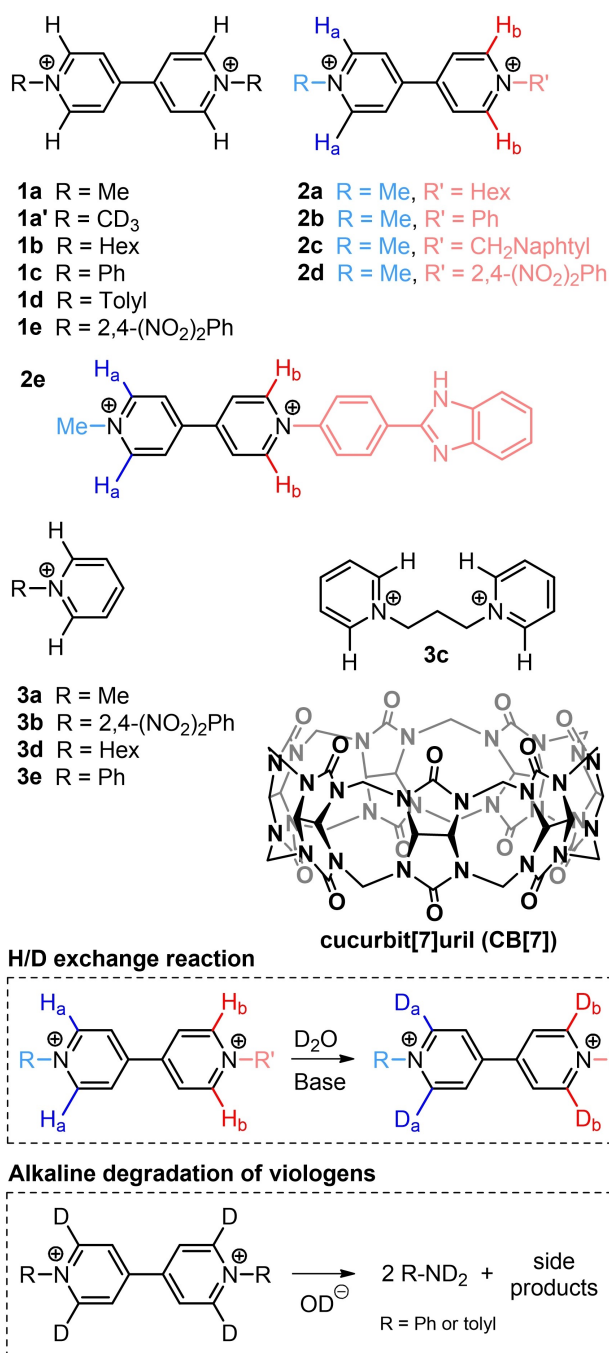
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Supporting information for this article is available on the WWW under <https://doi.org/10.1002/ejoc.202400404>

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**Scheme 1.** Structures of viologens and pyridiniums studied for H/D exchange in this contribution (halide counter-anions are omitted, but described in Supporting Information), and of cucurbit[7]uril. Protons exchanged with deuterium atoms are highlighted in colour and labelled as H<sub>a</sub> and H<sub>b</sub>. H/D exchange reaction and the alkaline degradation of viologens are illustrated.

best of our knowledge. Here, we describe the reactivity of a series of alkyl and substituted phenyl viologens or pyridiniums in deuterated water at various basic pH. The H/D–C(2) exchange rates have been monitored over time by <sup>1</sup>H NMR spectroscopy, before investigating the protective effect of CB[7] on the selective deuteration of the studied viologen derivatives. Finally, the deuterated viologens were exploited to confirm the

fragmentation mechanism observed during ESI-MS experiments.

## Results and Discussion

### Synthesis and Supramolecular Complexes

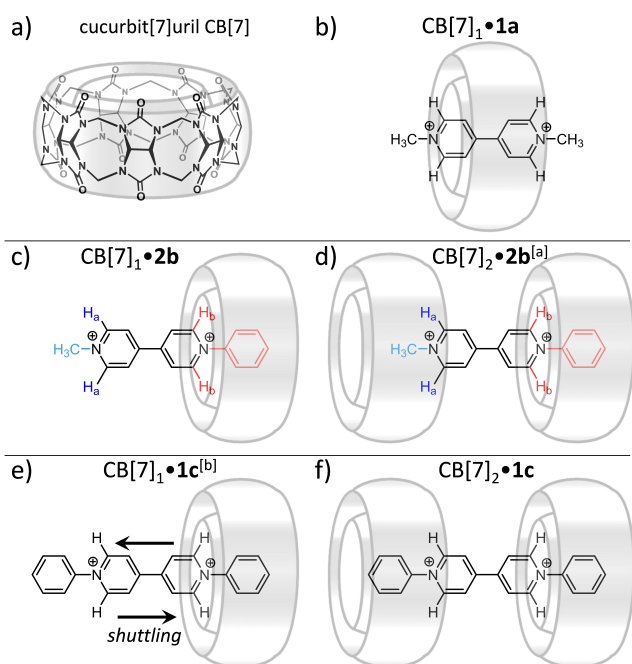
Alkyl-viologens and alkyl-pyridiniums were synthesized by nucleophilic substitutions from 4,4'-bipyridine or pyridine and the corresponding alkyl halide, while the phenyl viologens were prepared by Zincke reaction<sup>[24]</sup> from a 2,4-dinitrophenyl-viologen precursor. The reaction of 4,4'-bipyridine and a large excess of ICD<sub>3</sub> led to viologen **1a'**. Dissymmetric viologens **2a** and **2c** were prepared via reaction of methyl iodide on 1-hexyl-4-(4-pyridyl)pyridinium or 1-naphthylmethyl-4-(4-pyridyl)pyridinium. Viologen **2e** was prepared according to the literature.<sup>[25]</sup> The Zincke reaction of **2d** and aniline gave the dissymmetric viologen **2b**. Details of the syntheses and characterizations can be found in the supporting information.

Single crystals of **2b** suitable for X-ray diffraction were obtained by evaporation of an ethanol solution of the viologen (Figure S3, SI) confirming the expected molecular structure.<sup>[26]</sup> Compared to similar 4-methyl,4'-bis/tris-phenyl-viologen X-ray structures,<sup>[27]</sup> no stacking is observed between the two **2b** viologens of the unit cell.

Among all these viologens, substitutions by phenyl groups seemed to impact the most the H/D exchange, and so corresponding viologens were further studied in the presence of CB[7]. For viologens carrying small hydrophobic groups such as methyl groups (**1a**), CB[7] sits on the central 4,4'-bipyridinium moiety (Scheme 2b).<sup>[16]</sup> For the dissymmetric methyl-phenyl-viologen **2b**,<sup>[28]</sup> the <sup>1</sup>H NMR titration (Figure S8, SI) confirmed the phenyl inclusion in the macrocycle cavity but a slight CB[7] excess (1.5 equiv., Figure S8, SI) would be required to obtain the well-defined CB[7]•**2b** complex (Scheme 2c). This phenomenon could be due to a competition between a CB[7] complexation on the Ph-N<sup>+</sup> station and the viologen station (host shuttling with favoured residence on the Ph–N<sup>+</sup> station). The interaction of a second CB[7] on CB[7]•**2b** would render the viologen station unfavourable, thereby stabilizing the phenyl complexation. Actually, addition of a large excess of host (up to 5.2 equiv. of CB[7], Figure S8, SI) showed a –CH<sub>3</sub> upfield shifted signal, accompanied by downfield shifted signals of bipyridinium protons (Figure S8, SI), and suggested the methyl inclusion in a CB[7]<sub>2</sub>•**2b** complex (Scheme 2d).

When two large groups are introduced such as aromatic groups, CB[7] prefers to sit aside the central dicationic group, and peripheral complexations by CB[7] are frequently observed.<sup>[29]</sup> For **1c**, one equivalent of host results in a CB[7]<sub>1</sub>•**1c** molecular shuttle (Scheme 2e) featured by one CB[7] autonomously shuttling between the two peripheral phenyl groups.<sup>[13b]</sup> Finally, excess host showed NMR spectra in accord with a CB[7]<sub>1</sub>•**1c** host•guest complex (Scheme 2f).<sup>[30]</sup>

NMR spectra of CB[7] complexes of these three viologens were recorded and then fully assigned by a combination of COSY and NOESY <sup>1</sup>H–<sup>1</sup>H NMR spectroscopy experiments (SI).



**Scheme 2.** Molecular structures of the studied CB[7] complexes of viologens **1a**, **2b** and **1c**. [a] The well-defined complex CB[7]<sub>2</sub>•**2b** having a CB[7] on methyl and phenyl group was observed with a large excess of CB[7] (Figure S8, SI). [b] a shuttling system (CB[7] translocation between the two phenyl group) was observed for complex CB[7]<sub>1</sub>•**1c** (Figure S7a, SI).

### H/D Exchange Rate of Free Viologens

The H/D exchange reaction (Equation (1)) for the viologens considered (Scheme 1) has been studied by <sup>1</sup>H NMR in D<sub>2</sub>O alkaline solutions, following the method of Edwards et al (Figure S1, SI).<sup>[18]</sup> In this contribution, an identical initial concentration of viologen derivatives of 1.0 mM was used for the kinetic experiments with NaOH, K<sub>2</sub>CO<sub>3</sub> or NaHCO<sub>3</sub> as alkaline species. Considering the large excess of D<sub>2</sub>O and the constant concentrations with time of the alkaline species, we determined the rate constants as *k*<sub>obs</sub> in concentrations of exchangeable protons (noted *H*<sub>*x*</sub> in Equation (2)). The plots of ln[*H*<sub>*x*</sub>] against time were linear (Figure S10 and Table S1, SI), confirming the first order of the H/D kinetic reaction (Equation (3)).<sup>[18]</sup>



$$-d[Hx]/dt = k_{obs} \times [Hx] \quad (2)$$

$$\ln[Hx] = k_{obs} \times t + \text{constant} \quad (3)$$

In the presence of 10 equiv. of NaOH (pHexp = 12.42), the H/D exchange rate *k*<sub>obs</sub> of dimethylviologen **1a** was 3.5 × 10<sup>-4</sup> s<sup>-1</sup>. With 1 and 10 equiv. of K<sub>2</sub>CO<sub>3</sub> (pHexp of 10.71 and 11.25 respectively, Table 1), the full H/D exchange was achieved after several days and respective *k*<sub>obs</sub> values of 2.3 × 10<sup>-6</sup> s<sup>-1</sup> and 8.8 × 10<sup>-6</sup> s<sup>-1</sup> were determined. These values are in good agreement with the results of Edwards et al. (Figure S10, SI).<sup>[18]</sup> The same procedure was then applied on our viologens series to

**Table 1.** H/D exchange rate constants of viologen derivatives in D<sub>2</sub>O alkaline solutions.<sup>[a]</sup>

viologen	base	Base conc. (mM)	pH[b]	<i>k</i> <sub>obs</sub> (s <sup>-1</sup> )	t <sub>1/2</sub> (h)
<b>1a</b>	NaOH	10	12.56	3.5 × 10 <sup>-4</sup>	0.55
<b>1a</b>	K <sub>2</sub> CO <sub>3</sub>	10	11.25	8.8 × 10 <sup>-6</sup>	22
<b>1a</b>	K <sub>2</sub> CO <sub>3</sub>	1	10.71	2.3 × 10 <sup>-6</sup>	83.5
<b>1b</b>	NaOH	10	12.50	2.3 × 10 <sup>-4</sup>	0.85
<b>1b</b>	K <sub>2</sub> CO <sub>3</sub>	10	11.09	3.9 × 10 <sup>-6</sup>	49.5
<b>1b</b>	K <sub>2</sub> CO <sub>3</sub>	1	10.46	1.3 × 10 <sup>-6</sup>	148
<b>1c</b>	K <sub>2</sub> CO <sub>3</sub>	10	10.98	5.1 × 10 <sup>-4</sup>	0.4
<b>1d</b>	K <sub>2</sub> CO <sub>3</sub>	10	11.21	4.2 × 10 <sup>-5</sup>	4.5
<b>1d</b>	K <sub>2</sub> CO <sub>3</sub>	1	10.31	1.5 × 10 <sup>-5</sup>	13
<b>1e</b>	K <sub>2</sub> CO <sub>3</sub>	1	10.37	Fast degradation	
<b>2a</b>	NaOH	10	12.39		
<i>H</i> <sub><i>a</i></sub> <sup>[c]</sup> :				2.2 × 10 <sup>-4</sup>	0.9
<i>H</i> <sub><i>b</i></sub> <sup>[d]</sup> :				1.9 × 10 <sup>-4</sup>	0.7
<b>2a</b>	K <sub>2</sub> CO <sub>3</sub>	10	11.08		
<i>H</i> <sub><i>a</i></sub> :				3.7 × 10 <sup>-6</sup>	52
<i>H</i> <sub><i>b</i></sub> :				3.0 × 10 <sup>-6</sup>	64
<b>2a</b>	K <sub>2</sub> CO <sub>3</sub>	1	10.75		
<i>H</i> <sub><i>a</i></sub> :				2.2 × 10 <sup>-6</sup>	87.5
<i>H</i> <sub><i>b</i></sub> :				1.9 × 10 <sup>-6</sup>	101.5
<b>2b</b>	NaOH	10	12.20		
<i>H</i> <sub><i>a</i></sub> <sup>[c]</sup> :				3.3 × 10 <sup>-4</sup>	0.6
<i>H</i> <sub><i>b</i></sub> <sup>[c]</sup> :				Very fast	
<b>2b</b>	K <sub>2</sub> CO <sub>3</sub>	10	10.97		
<i>H</i> <sub><i>a</i></sub> :				1.6 × 10 <sup>-5</sup>	12
<i>H</i> <sub><i>b</i></sub> :				1.95 × 10 <sup>-4</sup>	1.0
<b>2b</b>	K <sub>2</sub> CO <sub>3</sub>	1	10.41		
<i>H</i> <sub><i>a</i></sub> :				2.9 × 10 <sup>-6</sup>	7
<i>H</i> <sub><i>b</i></sub> :				2.7 × 10 <sup>-5</sup>	66.5
<b>2c</b>	K <sub>2</sub> CO <sub>3</sub>	1	10.60		
<i>H</i> <sub><i>a</i></sub> <sup>[c]</sup> :				3.3 × 10 <sup>-6</sup>	58.5
<i>H</i> <sub><i>b</i></sub> <sup>[c]</sup> :				1.1 × 10 <sup>-5</sup>	17.5
<b>2d</b> <sup>[d]</sup>	K <sub>2</sub> CO <sub>3</sub>	10	-	Very fast	
<b>2d</b>	NaHCO <sub>3</sub>	10	8.25	4.1 × 10 <sup>-6</sup>	47
<b>2e</b> <sup>[e]</sup>	-	-	7.32	1.4 × 10 <sup>-7</sup>	1370
<b>2e</b> <sup>[h]</sup>	NaHCO <sub>3</sub>	10	8.69	2.8 × 10 <sup>-6</sup>	7

[a] Conditions: H/D exchange experiments were monitored by <sup>1</sup>H NMR on 1 mM solutions of viologens at 25 °C (all data, including <sup>1</sup>H NMR spectra and calculations are presented in SI "8/H/D exchange kinetic experiments of viologens" and Table S2). [b] pH values were measured after kinetic experiments. [c] *k*<sub>obs-*H*<sub>*a*</sub></sub> values evaluated on *H*<sub>*a*</sub>-C(2) group in β position of N-methyl group and *k*<sub>obs-*H*<sub>*b*</sub></sub> values evaluated on *H*<sub>*b*</sub>-C(2) group in β position of N-R' group (Scheme 1). [d] *k*<sub>obs-*H*<sub>*b*</sub></sub> values evaluated on *H*<sub>*b*</sub>-C(2) group in β position of N-phenyl(NO<sub>2</sub>)<sub>2</sub> group. [e] *k*<sub>obs</sub> determined on H-C(2) in β of phenylene group.

explore the substituent effect on the H/D exchange rates. The H/D exchange kinetics of dihexyl-substituted viologen **1b** afforded slightly lower rate constants (*k*<sub>obs</sub> = 2.3 × 10<sup>-4</sup> s<sup>-1</sup>,

$1.3 \times 10^{-6} \text{ s}^{-1}$  or  $3.9 \times 10^{-6} \text{ s}^{-1}$  in the presence of 10 equiv. of NaOH, 1 or 10 equiv. of  $\text{K}_2\text{CO}_3$ , respectively, Table 1).

Conversely, viologens bearing poorly electron donating groups such as phenyl (**1c**) or tolyl (**1d**) proved to be unstable with 10 equiv. of NaOH. Under these rather strong alkaline conditions, solutions of **1c** (Figure S12a, SI) and **1d** (Figure S12b, SI) changed with time and formation of aniline or 4-methylaniline, respectively, was observed by  $^1\text{H}$  NMR spectroscopy. However, in the presence of 10 equiv. of  $\text{K}_2\text{CO}_3$ , *N,N'*-diphenylviologen **1c** and *N,N'*-ditolylviologen **1d** featured different H/D exchange rates of  $5.1 \times 10^{-4} \text{ s}^{-1}$  and  $4.2 \times 10^{-5} \text{ s}^{-1}$ , respectively (pH of 10.98 and 11.21, respectively). The bis(dinitrophenyl)viologen **1e** proved to be highly unstable in alkaline solutions and led to an immediate dark precipitate after addition of  $\text{K}_2\text{CO}_3$  or  $\text{NaHCO}_3$  solutions.

Then we investigated the H/D exchange of a series of asymmetric *N*-methylviologens (Scheme 1) bearing a hexyl (**2a**), phenyl (**2b**), 1-naphthylmethyl (**2c**) or 2,4-dinitrophenyl (**2d**) group in alkaline  $\text{D}_2\text{O}$  solutions. At pH = 10.75, the two protons in  $\beta$  of  $\text{N}^+\text{-Me}$  ( $\text{H}_a$ ) and in  $\beta$  of  $\text{N}^+\text{-Hex}$  ( $\text{H}_b$ ) of **2a** showed very similar H/D exchange rates ( $2.2 \times 10^{-6} \text{ s}^{-1}$  and  $1.9 \times 10^{-6} \text{ s}^{-1}$ , respectively, Table 1), reflecting a similar substituent effect of methyl and hexyl on the acidity of their respective H-C(2) centers. In contrast, a significant difference of H/D exchange rates was observed between the two H-C(2) groups of **2b** and **2c** in alkaline solutions. As observed during the kinetic experiments of **2b**, the H/D exchange rates are affected by the opposite viologen substituent, making the H-C(2) group in  $\beta$  of the  $\text{N}^+\text{-Me}$ , deuterated *faster* ( $k_{\text{obs-Ha}} = 1.6 \times 10^{-5} \text{ s}^{-1}$  with 10 equiv. of  $\text{K}_2\text{CO}_3$ , Table 1) than the corresponding group of *N,N*-dimethylviologen **1a** ( $k_{\text{obs}} = 8.8 \times 10^{-6} \text{ s}^{-1}$  with 10 equiv. of  $\text{K}_2\text{CO}_3$ , Table 1). Simultaneously, this also resulted in a deuteration of the H-C(2) group in  $\beta$  of the  $\text{N}^+\text{-Ph}$  ( $k_{\text{obs-Ha}} = 1.95 \times 10^{-4} \text{ s}^{-1}$  with 10 equiv. of  $\text{K}_2\text{CO}_3$ , Table 1) *slower* than the one observed for *N,N*-diphenylviologen **1c** ( $k_{\text{obs}} = 5.1 \times 10^{-4} \text{ s}^{-1}$  with 10 equiv. of  $\text{K}_2\text{CO}_3$ , Table 1).

Studied with 1 equiv. of  $\text{K}_2\text{CO}_3$ , the 1-naphthylmethyl group of **2c** made the H/D exchange of the H-C(2) group in  $\beta$  of the  $\text{N}^+\text{-Me}$  *faster* ( $k_{\text{obs-Ha}} = 3.3 \times 10^{-6} \text{ s}^{-1}$  compared to  $k_{\text{obs}} = 2.3 \times 10^{-6} \text{ s}^{-1}$  for the H/D exchange in methyl-viologen **1a**, Table 1). Since **2d** was unstable in  $\text{K}_2\text{CO}_3$  solution, the H/D exchange reactions were explored using 10 equiv. of  $\text{NaHCO}_3$ . Under these conditions, the H-C(2) group in  $\beta$  position of the

dinitrobenzene function was fully deuterated in few hours ( $k_{\text{obs-Hb}} = 4.1 \times 10^{-6} \text{ s}^{-1}$ ), while the second H-C(2) group ( $\text{H}_a$ , in  $\beta$  position of  $\text{Me-N}^+$ , Scheme 1) was unchanged, even after several days. Notably, the proton in  $\alpha$  position of the two  $\text{NO}_2\text{-C}$  groups (labeled  $\text{H}_c$  in SI) was partially exchanged by deuterium.

Globally, it appears that two alkyl groups (**1a** and **1c**, Table 1) tend to decelerate the H/D exchange of pyridinium H-C(2) protons, while two aromatic groups (**1c** and **1d**, Table 1) tend to accelerate this H/D exchange. A hybrid situation is observed for mixed alkyl/aromatic functionalized viologens.

Finally a methylphenylviologen **2e** bearing a benzimidazole function was studied in  $\text{D}_2\text{O}$ .

The imidazole acted as a very soft base ( $\text{p}K_a = 4.0$ )<sup>[17a]</sup> and induced a slow H/D exchange of the H-C(2) group in  $\beta$  of the  $\text{N}^+\text{-Ph}$  group ( $k_{\text{obs}} = 1.4 \times 10^{-7} \text{ s}^{-1}$ , Table 1), while H-C(2) group in  $\beta$  of the  $\text{N}^+\text{-Me}$  group remained unchanged. In presence of 10 equiv. of  $\text{NaHCO}_3$ , the H/D exchange rate increased to  $2.8 \times 10^{-6} \text{ s}^{-1}$ . Whereas the imidazole group promoted the deuteration of **2e**, the excess of weak base such as  $\text{NaHCO}_3$  accelerated the H/D exchange. Notably, stronger bases including  $\text{K}_2\text{CO}_3$  caused the immediate degradation of **2e**.

The kinetic experiments in  $\text{D}_2\text{O}$  alkaline solutions were expanded to a series of pyridinium compounds (see Table 2).

In the presence of 10 equiv. of NaOH, the H/D exchange rate of the H-C(2) group of **3a** was significantly slower ( $k_{\text{obs}} = 3.5 \times 10^{-6} \text{ s}^{-1}$ ) than the corresponding one in **1a** ( $k_{\text{obs}} = 3.5 \times 10^{-4} \text{ s}^{-1}$ ), confirming the stronger stability of pyridinium species compared to viologens. The  $\text{D}_2\text{O}$  solution of **3b** with 10 equiv. of  $\text{NaHCO}_3$  showed both H/D exchange of the H-C(2) group ( $k_{\text{obs}} = 3.9 \times 10^{-6} \text{ s}^{-1}$ ), and of the  $\beta$  proton of the two  $\text{C-NO}_2$  moieties ( $k_{\text{obs}} = 1.4 \times 10^{-6} \text{ s}^{-1}$ ).

However, the addition of  $\text{K}_2\text{CO}_3$  to pyridinium **3b** led to a very fast degradation and formation of a red precipitate.

Finally, the addition of 10 equiv. of  $\text{K}_2\text{CO}_3$  or NaOH to **3c** in  $\text{D}_2\text{O}$  led to H/D-C(2) exchange with respective rate constants of  $k_{\text{obs}} = 9.1 \times 10^{-7} \text{ s}^{-1}$  and  $3.2 \times 10^{-5} \text{ s}^{-1}$ , which are significantly higher than the rates observed for **3a** ( $k_{\text{obs}} = 3.5 \times 10^{-6} \text{ s}^{-1}$ , Table 1).

This kinetic study illustrates the crucial effect of substituents on the nitrogen atoms of this series of viologen and pyridinium derivatives on the H/D exchange of the H-C(2) groups in alkaline deuterated water. According to Edwards et al.,<sup>[18]</sup> the alkaline species acts as a catalyst in the H/D exchange reaction,

**Table 2.** H/D exchange rate constants of pyridinium derivatives in  $\text{D}_2\text{O}$  alkaline solutions.<sup>[a]</sup>

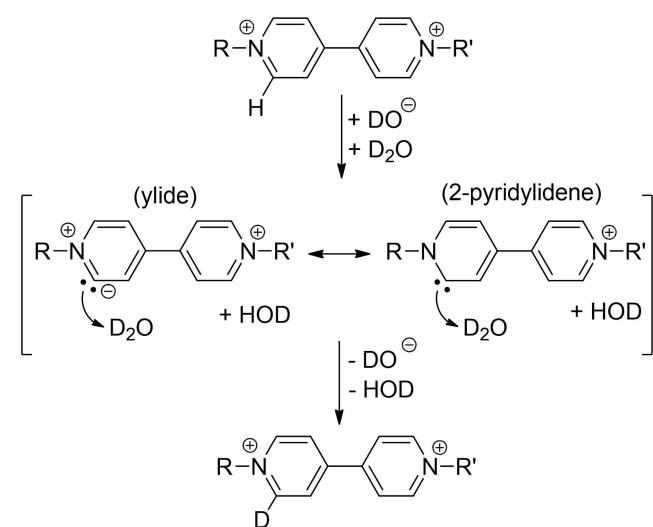
Pyridinium	base	Base concentration (mM)	pH[b]	$k_{\text{obs}}$ ( $\text{s}^{-1}$ )	t1/2 (h)
<b>3a</b>	NaOH	10 mM	12.62	$3.5 \times 10^{-6}$	55
<b>3a</b>	$\text{K}_2\text{CO}_3$	1 mM	10.72	$2.3 \times 10^{-7}$	83.5
<b>3b</b>	$\text{K}_2\text{CO}_3$	10 mM	11.09	Fast degradation	
<b>3b</b>	$\text{NaHCO}_3$	10 mM	8.90	$3.9 \times 10^{-6}$	49.5
<b>3c</b>	$\text{K}_2\text{CO}_3$	10 mM	11.05	$9.1 \times 10^{-7}$	212
<b>3c</b>	NaOH	10 mM	12.65	$3.2 \times 10^{-5}$	6

[a] Conditions: H/D exchange experiments were monitored by  $^1\text{H}$  NMR on 1 mM solutions of pyridiniums at 25 °C (all data, including  $^1\text{H}$  NMR spectra and calculations are presented in SI "9/H/D exchange kinetic experiments of pyridiniums" and Table S3). [b] pH values were measured after kinetic experiments.

and is so involved in the generation of intermediates at key states (Scheme 3).

Ratts et al. claimed the formation of ammonium ylide compounds after basic deprotonation of pyridiniums,<sup>[31]</sup> which is an usual way to produce carbene derivatives (2-pyridylidene).<sup>[32]</sup>

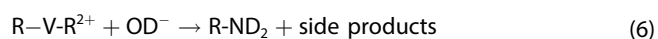
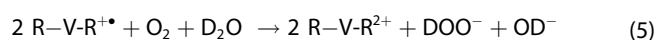
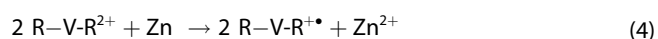
Finally the intermediate is most likely a deprotonated viologen having a hybrid structure between a ylide and a 2-pyridylidene (Scheme 3). *N*-substituents such as alkyl (methyl, hexyl) are expected to electronically enrich the ammonium and so disfavor the formation of the ylide intermediate. Since the formation of the intermediate requires more energy, the reaction is less favored and the observed H/D exchange is slower. In contrast, aromatic substituents (phenyl, tolyl) are expected to stabilize deprotonated intermediates and, as observed, increase the H/D exchange rates. However, the ylide should in principle be sensitive to oxygen, which could lead to the oxidation of viologens into pyridines.<sup>[33]</sup> This can explain the fast degradation of the diaromatic viologens in strong alkaline conditions. In this case, we observed a rapid degradation of diaromatic viologens **1c** and **1d** and identified aniline and *p*-methylaniline as respective degradation products. The rest of the viologen skeleton could be oxidized.<sup>[33]</sup> Indeed viologens carrying aromatic electron withdrawing groups such as **1e** are unstable in water. Concerning pyridiniums, we can note a significant difference for the H/D exchange rates between the methylpyridinium **3a** and the dipyridinium **3c** in the presence of 10 equiv. of NaOH ( $k_{\text{obs}}=3.5\times 10^{-6}$  and  $k_{\text{obs}}=3.2\times 10^{-5}$  s<sup>-1</sup>, respectively). This could be due to a ring closure reaction from a nucleophilic attack of the adjacent deprotonated pyridinium resulting in a stabilized intermediate (Figure S11, SI). Such reaction has been described for bispyridinium analogues featured by propyl or butyl spacer which were shown to react with strong bases (NaH) in organic media to afford bipyridinylidenes.<sup>[34]</sup>



**Scheme 3.** Proposed H/D exchange mechanism occurring on viologens in D<sub>2</sub>O alkaline solutions.

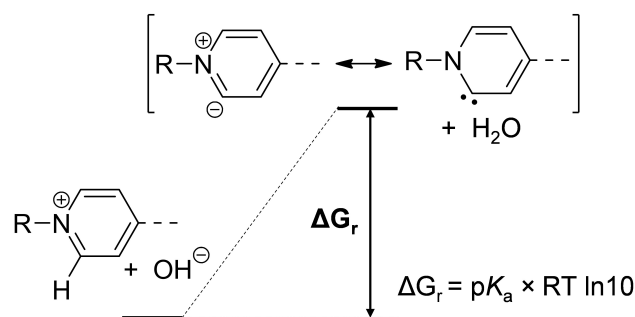
Indeed, Murphy et al. confirmed that the H-C(2) group of *N*-propyl-bridged bis(dimethylaminopyridinium) can be fully deuterated in D<sub>2</sub>O using a soft base (NEt<sub>3</sub>).<sup>[35]</sup>

Since the radical cation of viologens has been suggested to play a role in the degradation mechanism,<sup>[9,36]</sup> we explored the reduction of the prepared viologen in D<sub>2</sub>O solution. Vaid and coworkers showed that zinc is an efficient reductant of bis-aryl viologens into neutral species in ethanol under inert atmosphere.<sup>[37]</sup> In this contribution, we studied the Zn reduction of **1a**, **1c**, **1d** and **2b** in D<sub>2</sub>O solution under air. The contact of Zn suspension with **1a** led to a blue solution, which is characteristic of the radical cation of dimethyl viologen (Equation (4)),<sup>[38]</sup> but the coloration disappeared under stirring, probably due to oxidation by O<sub>2</sub> (Figure S13a, SI). No coloration was observed in the solutions containing Zn and **1c**, **1d** or **2b**. However, after 16 h under stirring, a dark deposit was observed and NMR analysis of the solution after filtration revealed the formation of aniline from the **1c** and **2b** solutions (Figures S13b and d, SI) and 4-methylaniline from the **1d** solution (Figure S13c, SI). Rieger et al. hypothesized that the O<sub>2</sub> oxidation of radical cationic viologen would lead to hydroxide (Equation (5)).<sup>[9]</sup> Since **1c**, **1d** and **2b** are highly reactive toward basic species, they rapidly evolved toward anilines (Equation (6)).



### DFT Calculated pK<sub>a</sub> of Free Viologens

The experimental pK<sub>a</sub> values of the studied viologen, higher than 14, cannot be evaluated in water. However the DFT calculation of Gibbs energy of an acid dissociation is an elegant way to estimate the theoretical pK<sub>a</sub> of the reaction.<sup>[39]</sup> Hypothesizing that the viologen or pyridinium deprotonation results in a ylide/2-pyridylidene intermediate before deuteration (Figure 1), we extrapolated the intermediate as a deprotonated



**Figure 1.** Theoretical calculations of Gibbs energy  $\Delta G_r$  and theoretical pK<sub>a</sub> based on an ylide/2-pyridylidene intermediate during the H/D exchange process of pyridiniums or viologens.

species to calculate the corresponding Gibbs energy of the deprotonation reaction by DFT (Tables S2 and S3, SI).

Computed  $pK_a$  values are summarized in Table 3 after geometry optimization of the considered molecules using the Gaussian 16 software package,<sup>[40]</sup> and employing the M06-2X functional<sup>[41]</sup> in combination with the 6-31 + G(d,p) basis set.<sup>[42]</sup>

A Gibbs energy of 22.6 kJ mol<sup>-1</sup> to deprotonate viologen **1a** was calculated, leading to a theoretical  $pK_a$  value of 18.0 and confirming the relative high stability of its H–C(2) bond in alkaline conditions. In contrast, the low reaction energies calculated for the H–C(2) groups of **1c** and **1d** (15.4 and 15.7 kJ mol<sup>-1</sup>, respectively, Table 3) are in good agreement with their observed high H/D exchange rates. The calculation method provided a negative value of –1.8 kJ mol<sup>-1</sup> for the deprotonation of **1e**, in agreement with the lability of its H–C(2) protons and its low stability in water. Interestingly, the calculations on **2b** permitted to assess two different Gibbs energies of 26.6 and 16.3 kJ mol<sup>-1</sup> (Table 3) corresponding respectively to the H<sub>a</sub> and H<sub>b</sub> deprotonations (Scheme 1), which also give two different experimental H/D exchange rates (Table 1).

The higher energy required for the H<sub>b</sub> deprotonation of **2b** (in  $\beta$  of Ph–N<sup>+</sup>, Scheme 1) compared to the one of the symmetric viologen **1c** (15.4 kJ mol<sup>-1</sup>, Table 3) was in good agreement with the lower H/D experimental rate observed for **2b** with respect to that for **1c** (in presence of 10 equiv. of K<sub>2</sub>CO<sub>3</sub>,  $k_{\text{obs-Hb}}$  of **2b**: 1.95 × 10<sup>-4</sup>,  $k_{\text{obs}}$  of **1c**: 5.1 × 10<sup>-4</sup> s<sup>-1</sup>, Table 1).

However calculations showed a significant higher H<sub>a</sub>/D<sub>a</sub> exchange energy for **2b** (26.6 kJ mol<sup>-1</sup>) than for **1a** (22.6 kJ mol<sup>-1</sup>, Table 3), while their experimental rate constants are in the same order of magnitude (Table 1).

The Gibbs energy calculations applied on pyridiniums confirmed their lower reactivity toward deprotonation compared to those involving viologens. *N*-alkyl-pyridinium **3a** and **3d** are featured by an identical  $pK_a$  value of 21, while the *N*-phenyl-pyridinium **3e** shows a lower  $pK_a$  value of 19.4. In accord with experiments, **3b** was the most reactive compound of the pyridinium series toward alkaline solutions (Gibbs energy of 11.7 kJ mol<sup>-1</sup> and calculated  $pK_a$  value of 16.0), but much more stable than its bis-(2,4-dinitrophenyl)-viologen analogue **1e**.

Molecule	$\Delta G_r$ (kJ/mol)	$pK_a$
<b>1a</b>	22.6	18.0
<b>1c</b>	15.4	16.7
<b>1d</b>	15.7	16.7
<b>1e</b>	–1.8	13.7
<b>2b</b> , H <sub>a</sub> (methyl moiety)	26.6	18.7
H <sub>b</sub> (Phenyl moiety)	16.3	16.8
<b>3a</b>	40.0	21.0
<b>3b</b>	11.7	16.0
<b>3d</b>	40.0	21.0
<b>3e</b>	31.0	19.4

## Mass Spectrometry of Deuterated Viologens

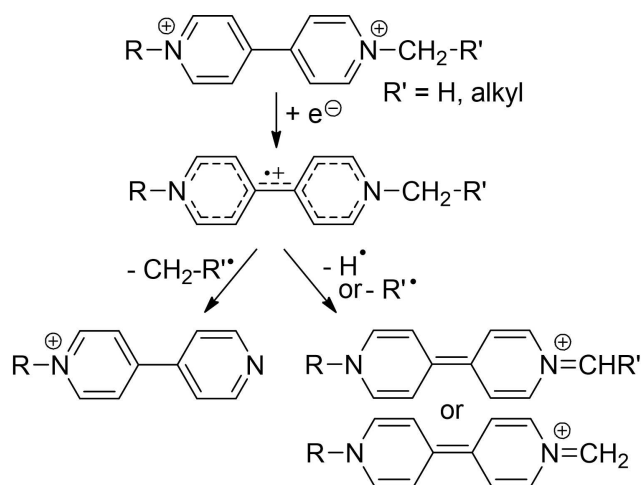
Mass spectrometry is an elegant method to study the viologen rearrangements in gas phase. Mass spectra of dialkylviologens highlighted the loss of {H<sup>+</sup>} during the analytic process, probably via a two step mechanism involving successively a one electron reduction of viologen and then a proton elimination, leading to iminiums (Scheme 4).<sup>[11,43]</sup>

Of note, the viologen one electron reduction would also lead to an alkyl fragmentation (Scheme 4).<sup>[11,44]</sup>

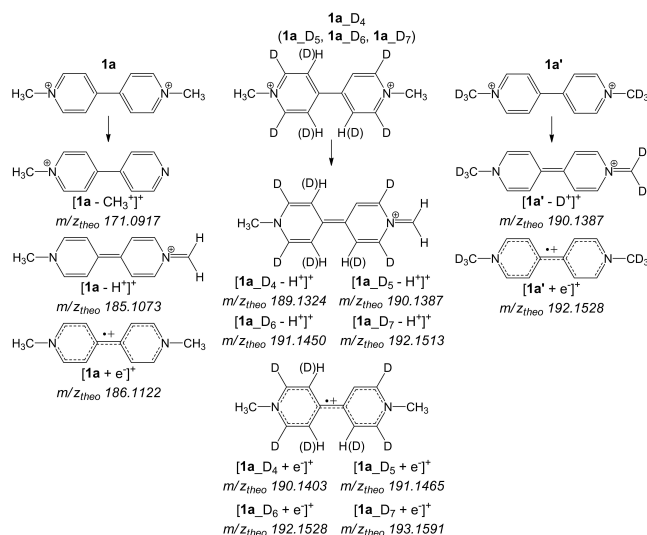
In this context, we analyzed the mass spectra of the viologen series by electrospray in acetonitrile to discriminate the source of the {H<sup>+</sup>} elimination, between protons of the viologen core or protons of viologen substituents.

The mass spectrum of **1a** (Figure S14, SI) showed the formation of the cations resulting from a one electron reduction ( $m/z$  186.1152), a {H<sup>+</sup>} elimination ( $m/z$  185.1074), and a {H<sub>3</sub>C<sup>+</sup>} elimination ( $m/z$  171.0920), in addition of the unmodified [1a]<sup>2+</sup> signal ( $m/z$  93.0572) as the main peak of the spectrum (Scheme 5).

Since our kinetic experiments showed the high lability of H–C(2) in alkaline D<sub>2</sub>O solutions, we investigated the gas phase behavior of the deuterated **1a** (noted “**1a**\_D<sub>x</sub>”, Scheme 5), obtained from **1a** in a D<sub>2</sub>O solution with 1 equiv. of K<sub>2</sub>CO<sub>3</sub> after 22 days. The mass spectrum showed the formation of **1a**\_D<sub>4</sub>, **1a**\_D<sub>5</sub>, **1a**\_D<sub>6</sub> and **1a**\_D<sub>7</sub> ( $m/z$  95.0700, 95.5732, 96.0760 and 96.5788, respectively, Figure S15, SI) with similar intensities pointing to partial deuteration of H–C(3) protons (Scheme 5). The signal  $m/z$  189.1328 was attributed to the species [1a\_D<sub>4</sub>–H<sup>+</sup>]<sup>+</sup> (Scheme 5), indicating that, beside this additional deuteration, a proton must have been lost. The signals of [1a\_D<sub>x</sub>–e<sup>-</sup>]<sup>+</sup> species ( $x=4, 5, 6$  or  $7$ ) were identified. As a control, we prepared **1a'** bearing two –CD<sub>3</sub> groups (Scheme 5) and studied its behavior in the gas phase. The mass spectrum of **1a'** (Figure S16, SI) revealed the usual dialkylviologen decay products, i.e. the one electron reduction ( $m/z$  192.1529), a {D<sup>+</sup>}



Scheme 4. Proposed mechanism for {H<sup>+</sup>} elimination or *N*-alkyl substituents elimination observed on mass spectra of viologens.



**Scheme 5.** Proposed structures of **1a**, **1a<sub>x</sub>** ( $x=4, 5, 6, 7$ ) and **1a'** after rearrangement in gas phase.

elimination ( $m/z$  190.1386) and a  $\{D_3C^+\}$  elimination ( $m/z$  174.1105). Because **1a'** lost D atoms instead of H atoms, the mass spectra of **1a**, **1a<sub>D<sub>x</sub></sub>** and **1a'** confirmed that the main evolution concerns the alkyl groups in the gas phase (Scheme 4).

This contrasts with the high lability of the viologen H–C(2) groups observed in alkaline solutions. The mass spectrometry study was expanded to compounds **1c** (Figure S17, SI) and **1c<sub>D<sub>4</sub></sub>** (Figure S18, SI). The weak signals corresponding to the elimination of  $\{H^+\}$  or  $\{D^+\}$  from **1c** or **1c<sub>D<sub>4</sub></sub>**, respectively, confirmed the robustness of the bipyridine skeleton in gas phase. Finally, the mass spectra of **2e** and **2e<sub>D<sub>2</sub></sub>** (Figures S19 and S20, SI) showed minor signals resulting from a  $\{H^+\}$  or  $\{D^+\}$  elimination. The MS/MS experiment focusing on the main signals ( $m/z$  of 182.1 and 183.1, respectively for **2e** and **2e<sub>D<sub>2</sub></sub>**, Figure S21, SI) permitted to observe the release of a methylpyridinium-pyridine and phenyl-benzimidazole fragments.

The mass spectrometry of these viologens and deuterated viologens (obtained from deuteration in  $D_2O$  alkaline solutions) confirmed that, in the gas phase, fragmentations concern mainly the *N*-substituents, while the bipyridine core remain unchanged.

### H/D Exchange Rate of CB[7]\*Viologen Complexes

The high binding constants of CB[*n*] complexes are an important consequence of mainly (i) the release of high-energy water molecules and (ii) the strong hydrogen bonds between the carbonyl groups of CB[*n*] rims and pseudo-acidic protons of the guest, sometimes resulting in positive  $pK_a$  shifts.<sup>[45]</sup> Another consequence of the CB[*n*] complexation is a protective effect toward the guest acidic protons resulting in a significant decrease of the H/D exchange rates in alkaline  $D_2O$  solutions as observed for CB[7]\*bis(imidazolium) complexes.<sup>[22a,c]</sup> Because we

are interested in CB[*n*] complexes of viologens and have already studied a variety of such systems,<sup>[46]</sup> we decided to investigate how CB[7] complexation would impact the H/D exchange rates of viologens **1a**, **1c** and **2b** using different ratios of CB[7] to viologens. The results are presented in Table 4.

The H/D exchange rates of  $CB[7]_{0.5} \cdot 1a$  and  $CB[7] \cdot 1a$  were evaluated in  $D_2O$  solution (1 mM) in the presence of 10 equiv. of NaOH. Even in default, CB[7] complexation lowered the H/D exchange rates ( $k_{obs} = 3.6 \times 10^{-5} s^{-1}$  and  $6.4 \times 10^{-6} s^{-1}$ , with 0.5 and 1 equiv. of CB[7] respectively) compared to what observed for free **1a** ( $k_{obs} = 3.5 \times 10^{-4} s^{-1}$ ) with 10 equiv. of NaOH.

Then, we explored the influence of the  $CB[7]:1c$  ratio on the H/D exchange rate of **1c** in alkaline solutions. Viologen **1c** possesses two stations to accommodate CB[7],<sup>[28]</sup> but with 1 equiv. of host, CB[7] was observed to shuttle autonomously on the guest axle between the two phenyl sites (molecular shuttle, Scheme 2e). In fact, the CB[7] complexation of **1c** decreased the H/D exchange rate of viologen **1c** with 10 mM  $K_2CO_3$  by a factor of 25 ( $k_{obs} = 2.0 \times 10^{-5} s^{-1}$ , Table 4). Interestingly, in the  $CB[7]_1 \cdot 1c$  molecular shuttle, there is always, at a given time, a default of CB[7] with respect to accessible stations on the **1c** axle (the ratio of occupied versus unoccupied  $N^+$ -Ph groups is strictly 50/50).

Yet, CB[7] exerts a very significant effect on the global H/D exchange as the corresponding rate constant is reduced by a

**Table 4.** H/D exchange rates of  $CB[7] \cdot$ viologen complexes in  $D_2O$  alkaline solutions.<sup>[a]</sup>

Complex	Base	Base concentration	pH[b]	$k_{obs}$ (s <sup>-1</sup> )	t <sub>1/2</sub> (h)
$CB[7]_{0.5} \cdot 1a$	NaOH	10 mM	12.54	$3.6 \times 10^{-5}$	5.5
$CB[7]_1 \cdot 1a$	NaOH	10 mM	12.08	$6.4 \times 10^{-6}$	30
$CB[7]_1 \cdot 1c$	$K_2CO_3$	10 mM	11.01	$2.0 \times 10^{-5}$	9.5
$CB[7]_{0.5} \cdot 1c$	NaOH	10 mM	- <sup>[d]</sup>	$1.45 \times 10^{-3}$	0.15
$CB[7]_1 \cdot 1c$	NaOH	10 mM	- <sup>[d]</sup>	$7.9 \times 10^{-4}$	0.25
$CB[7]_2 \cdot 1c$	NaOH	10 mM	12.26	$1.35 \times 10^{-6}$	143
$CB[7]_1 \cdot 2b$	NaOH	10 mM	12.17		
$H_a$ <sup>[c]</sup>				$1.5 \times 10^{-4}$	1.3
$H_b$ <sup>[c]</sup>				$4.1 \times 10^{-4}$	0.5
$CB[7]_{1.5} \cdot 2b$	NaOH	10 mM	12.36		
$H_a$				$8.8 \times 10^{-5}$	2.2
$H_b$				$9.3 \times 10^{-6}$	20.5
$CB[7]_{1.5} \cdot 2b$	$K_2CO_3$	10 mM	- <sup>[d]</sup>		
$H_a$				$3.8 \times 10^{-6}$	50.5
$H_b$				$1.4 \times 10^{-6}$	137

[a] Conditions: H/D exchange experiments were monitored by  $^1H$  NMR on 1 mM solutions of viologens at 25 °C, the CB[7] concentrations were adjusted to the desired CB[7]:viologen ratios (all data, including  $^1H$  NMR spectra and calculations are presented in SI "12/H/D exchange kinetic experiments of CB[7]\*viologen complexes" and Table S6). [b] pH values were measured after kinetic experiments. [c]  $k_{obs-Ha}$  values evaluated on  $H_a$ -C(2) group in  $\beta$  position of *N*-methyl group and  $k_{obs-Hb}$  values evaluated on  $H_b$ -C(2) group in  $\beta$  position of *N*-phenyl group (Scheme 2). [d] pH measurements were performed a long time after reaction, but degradation of viologens into aniline consumed  $OH^-$  and  $OD^-$  (Equation (6)) and led to low pH values.



factor of 25, despite the absence of CB[7] on half of the stations at any time.

This remarkable improvement enabled to study the H/D exchange for **1c** with a stronger base. Indeed, while **1c** was unstable with NaOH, the addition of 0.5–2 equiv. of CB[7] permitted to observe and to determine the H/D exchange rates on this viologen in strong alkaline solutions. The addition of 0.5 equiv. of CB[7] (corresponding to a mixture of free **1c** and CB[7]<sub>1</sub>•**1c** molecular shuttle) led to a relative fast H/D exchange ( $k_{\text{obs}} = 1.45 \times 10^{-3} \text{ s}^{-1}$ ) but permitted to observe a fully H/D–C(2) deuterated **1c** complex without degradation in a 10 mM NaOH solution. Finally, the CB[7]:**1c** ratios of 1 (CB[7]<sub>1</sub>•**1c**, Scheme 2e) and 2 (CB[7]<sub>2</sub>•**1c**, Scheme 2f) led to  $k_{\text{obs}}$  values of  $7.9 \times 10^{-4} \text{ s}^{-1}$  and  $1.35 \times 10^{-6} \text{ s}^{-1}$  (Table 4), respectively, demonstrating a CB[7] control on H/D exchange rates, the double complexation (Scheme 2f) dramatically reducing the speed of H/D exchange by a factor of 600. This remarkable effect enabled to use CB[7] as a supramolecular protective group toward strong bases.

More interestingly, the use of CB[7] allowed to control the regioselectivity of the deuteration reaction of the dissymmetric viologen **2b** in an alkaline D<sub>2</sub>O solution. With 1 equiv. of host, CB[7] preferentially sits on the phenyl station of **2b** (Scheme 2c) and H<sub>a</sub>-C(2) and H<sub>b</sub>-C(2) groups exhibited H/D exchange rates of the same order of magnitude ( $k_{\text{obs-Ha}} = 1.5 \times 10^{-4} \text{ s}^{-1}$  and  $k_{\text{obs-Hb}} = 4.1 \times 10^{-4} \text{ s}^{-1}$ , Table 4) in a NaOH solution, in contrast to free **2b** (Figure 2). The CB[7]:**2b** ratio of 1.5 would stabilize the CB[7] inclusion of the N<sup>+</sup>-Ph station and optimized the protection of the H–C(2) group of the N<sup>+</sup>-Ph side (protons H<sub>b</sub>, Figure 2), making its H/D exchange rate slower ( $k_{\text{obs-Hb}} = 9.3 \times 10^{-6} \text{ s}^{-1}$ , Table 4) than the one corresponding to the N<sup>+</sup>-Me part (protons H<sub>a</sub>,  $k_{\text{obs-Ha}} = 8.8 \times 10^{-5} \text{ s}^{-1}$ , Table 4). In a 10 mM solution

of K<sub>2</sub>CO<sub>3</sub>, the difference in the H/D exchange rate between H<sub>a</sub>-C(2) and H<sub>b</sub>-C(2) of (CB[7])<sub>1.5</sub>•**2b** was confirmed (Table 4).

Therefore, the use of CB[7] as a supramolecular protecting group permitted to control the deuteration rates on the different positions H<sub>a</sub> or H<sub>b</sub> of **2b**. The presence of 1 equiv. of CB[7] adjusted the reactivity of H<sub>b</sub> protons toward deprotonation reaction to that of H<sub>a</sub> protons (Figure 2). Strikingly, with 1.5 equiv. of CB[7] we inverted the reactivity of H<sub>a</sub> and H<sub>b</sub> protons of **2b** (Figure 2). Finally suitable viologen:CB[7] ratios gave access to a regioselective deuteration of dissymmetric viologens.

## Conclusions

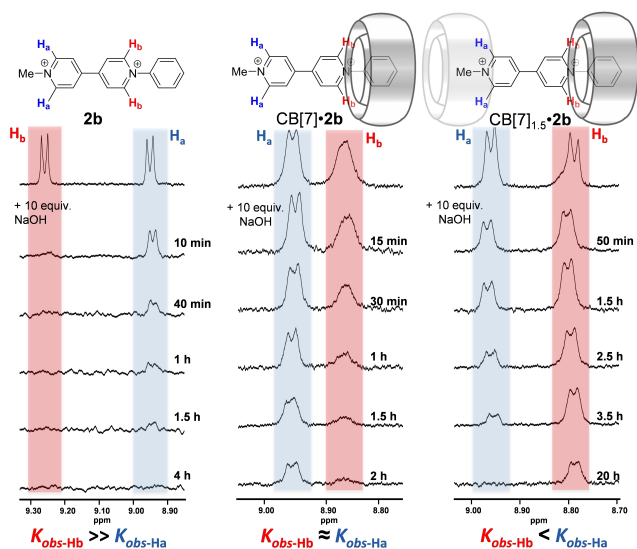
We established the H/D exchange rate constants of the H–C(2) part of a series of viologen compounds having various N-substituents and using different D<sub>2</sub>O alkaline solutions. N-dialkyl-viologens, including Paraquat (**1a**), are featured by slower H/D exchanges compared to N-diaryl-viologens pointing to the importance of the N-substituent electronic effects. Under strong alkaline conditions or in the presence of Zn as reductant, N-diaryl-viologens degraded into aniline derivatives. The dissymmetric viologen **2b** gave two distinct H/D exchange rate constants depending on its N-substituent (N<sup>+</sup>-Me or N<sup>+</sup>-Ph). Computational studies gave access to theoretical pK<sub>a</sub> values of the viologens and showed that high reactivities of H–C(2) groups toward basic species are achieved when N-substituents, such as aryl or 2,4-dinitrophenyl groups, stabilized deprotonated species and lowered the deprotonation energy.

While the reactivity in water is dominated by H/D exchanges for the four viologen H–C(2) groups, the reactivity in the gas phase is dominated by (i) single-electron viologen reduction and (ii) {H<sup>+</sup>} fragmentation at the corresponding N-alkyl substituents, while preserving the C–H bonds of the bipyridinium skeleton.

The addition of CB[7] resulted in strong host•guest complexes with viologens, which lowered H/D exchange rate constants of the H–C(2) groups in alkaline conditions, the host sterically shielding the viologens from their immediate surrounding. More interestingly, the optimized host:guest ratio of 1.5 to an alkaline solution of dissymmetric 1-methyl,1'-phenyl-viologen **2b** enhanced the protective effect of CB[7] on the included H<sub>b</sub>-C(2) group in β-position of N-phenyl (Scheme 2), making its reactivity toward H/D exchange reversed (H<sub>a</sub>/D exchange favored on Me side, Figure 2) compared to free **2b** (H<sub>b</sub>/D exchange favored on Ph side). We thus showed that the CB[7] macrocycle behaved as a supramolecular protecting group, providing regioselectivity for the viologen deuteration reaction.

Similarly, Appel and coworkers exploited the selective CB[7] inclusion of amine groups positioned on insulin to control their nucleophilicity for a regioselective PEG grafting.<sup>[47]</sup>

Utilization of macrocycles, including calix[6]arene,<sup>[48]</sup> resorcin[4]arene,<sup>[49]</sup> calix[4]pyrrole,<sup>[50]</sup> hexahomotrioxacalix[3]arene,<sup>[51]</sup> or Pillar[5]arene,<sup>[52]</sup> to promote a supramolecular protection of functional groups presents a



**Figure 2.** Regioselective deuteration of dissymmetric viologen **2b** in D<sub>2</sub>O (1 mM) in presence of 10 equiv. of NaOH, observed for free **2b** and complexes CB[7]<sub>1</sub>•**2b** and CB[7]<sub>1.5</sub>•**2b** (the pale grey CB[7] in CB[7]<sub>1.5</sub>•**2b** illustrates the partial complexation of the methyl site of **2b** in presence of 1.5 equiv. of CB[7]).

tremendous potential for organic synthesis and this strategy is now expanded with the use of cucurbit[7]uril. This supramolecular approach improves the stability of viologens in harsh conditions and opens new ways for selective viologen functionalizations.

## Experimental Section

The synthesis of viologens **1a–e** and **2a–d** and pyridiniums **3a–c** and their corresponding NMR spectra (including 1D and 2D NMR spectra, Figures S1–S5, SI) are fully described in Supporting Information. Viologen **2e** was prepared according to the literature.<sup>[25]</sup> The preparation and NMR characterization of the CB[7]\*viologen complexes are described in Supporting Information (Figures S6–S9, SI).

H/D exchange kinetic experiments were performed in NMR tubes from 1 mM D<sub>2</sub>O solutions of viologen or pyridiniums with the selected base (NaOH, K<sub>2</sub>CO<sub>3</sub> or NaHCO<sub>3</sub>) at 20 °C. H/D exchange rates were evaluated according to integrals of <sup>1</sup>H NMR. All kinetic experiments are presented in Supporting Information.

The DFT calculations of pK<sub>a</sub> and the accompanied theoretical structures are presented in Supporting Information (Tables S4 and S5, SI).

The viologens were analysed using a SYNAPT G2 HDMS mass spectrometer (Waters, Manchester, UK) equipped with a pneumatically assisted electrospray ionization (ESI) in dilution in acetonitrile. MS spectra of **1a**, **1a'**, **1a-D<sub>4</sub>**, **1c**, **1c-D<sub>4</sub>**, **2e** and **2e-D<sub>2</sub>** are showed in Supporting Information (Figures S14–S21, SI).

## Supporting Information Summary

Additional references cited within the Supporting Information.<sup>[53]</sup>

## Acknowledgements

CNRS and Aix-Marseille University are acknowledged for continuous support. We thank the French National Research Agency (ANR) for funding ANR-20-CE06-0016-01 (RadiCoord). This work received support through the AMUTech Institute, from the French government under the France 2030 investment plan, as part of the Initiative d'Excellence d'Aix-Marseille Université - A\*MIDEX.

## Conflict of Interests

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

**Keywords:** Viologen · Cucurbit[7]uril · Rate constant · Deuteration · Regioselectivity

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Manuscript received: April 13, 2024  
Revised manuscript received: June 9, 2024  
Accepted manuscript online: June 21, 2024  
Version of record online: July 30, 2024