Zwitterionic [4]helicene: a water-soluble and reversible pH-triggered ECD/CPL chiroptical switch in the UV and red spectral regions

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Simon Pascal,[a] Céline Besnard,[b] Francesco Zinna,[c] Lorenzo Di Bari,[c] Boris Le Guennic,[d] Denis Jacquemin,[e,f] and Jérôme Lacour*[a]

[a.] *University of Geneva, Department of Organic Chemistry, quai Ernest Ansermet 30, CH-1211 Geneva 4, Switzerland. E-mail: Jerome.lacour@unige.ch*
[b.] *Laboratory of Crystallography, University of Geneva, quai Ernest Ansermet 24, CH-1211 Geneva 4, Switzerland.*
[c.] *Università di Pisa, Dipartimento di Chimica e Chimica Industriale, Via G. Moruzzi 13, 56124 Pisa, Italy.*
[d.] *Institut des Sciences Chimiques de Rennes, UMR 6226 CNRS-Université de Rennes 1, 263 avenue du Général Leclerc, 35042 Rennes Cedex, France*
[e.] *Laboratoire CEISAM, UMR 6230 CNRS, Université de Nantes, 2 rue de la Houssinière, BP 92208, 44322 Nantes Cedex 3, France.*
[f.] *Institut Universitaire de France, 1, rue Descartes, F-75005 Paris Cedex 05, France*

The chiroptical switching properties of a readily accessible and water-soluble diaza [4]helicene are disclosed. This zwitterionic dye displays pH-dependent absorption and emission properties and this enables a reversible turn on/off of electronic circular dichroism at 300 nm and of circularly polarized luminescence in the red region upon protonation/deprotonation.

Strong efforts are currently devoted to the development of efficient chiroptical switches due to the potential applications in several fields, including catalysis, memory and light emitting devices, as well as molecular responsive probes.[1] Helicenes are particularly interesting patterns for the development of molecular switches due to their stable helical conformation and potentially pronounced chiroptical properties, *e.g.*, optical rotation, electronic circular dichroism (ECD) and circularly polarized luminescence (CPL).[2] Recently, a few examples of organic and organometallic helicenes demonstrated chiroptical switching under specific stimuli such as temperature variations,[3] ionic interactions[4] or redox transformations.[5] However, examples of pH-sensitive helicenes enabling chiroptical switching remain rare.[6] First of their kind, organometallic [6]helicenes **1** and **2** reported by Autschbach, Crassous and co-workers displayed ECD in the UV-blue range, Pt-[6]helicene **2** being in addition able to display CPL activity in the visible domain (Figure 1). More recently, Teplỳ and co-workers demonstrated possible ECD switching in the red region using organic [5]helicene **3** containing two hemicyanine motifs. In 2014, the study of quinacridinium **4** revealed an efficient pH-triggered absorption switching in the visible, however with moderate changes in fluorescence and ECD intensities. *N*,*N'*-Dialkyl diaza [4]helicenes of type **5** (Figure 2) remain of particular interest since they display fluorescence within the transparency window of biological media (*ca.* 680-1300 nm) and have proven their ability to selectively bind DNA.[7] Moreover, compound **5** (dipropyl) is prepared in only two steps from commercial 1,3-dimethoxybenzene (60% overall yield)[8] and can be isolated in an enantiopure form using proven resolution procedures.[9] Thanks to a high conformational stability ($\Delta G^{\ddagger}_{racem}$ ~42 kcal.mol^{-1}), helicene **5** can be furthermore handled at high temperature conveniently (<150 °C).

Within this context, the unique chiroptical properties in the UV and red domains of a readily accessible zwitterionic diaza [4]helicene **6** were investigated (Figure 2). As reported recently, this compound can be obtained by consecutive Vilsmeier-Haack and Pinnick reactions of **5** (65% yield over two steps).[10]
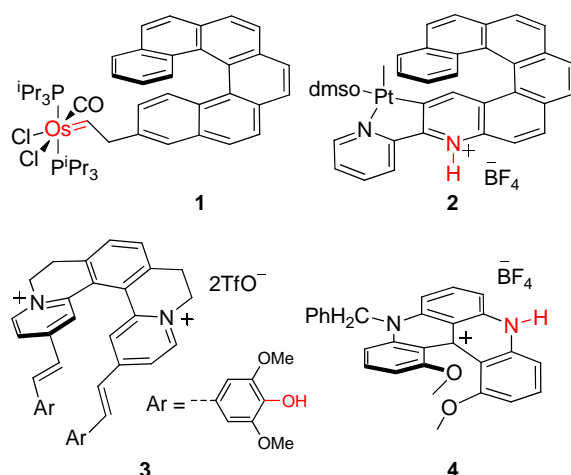
Figure 1. Previously reported pH-sensitive helicene-based chiroptical switches; only acidic and *P* enantiomer forms are represented.[6]
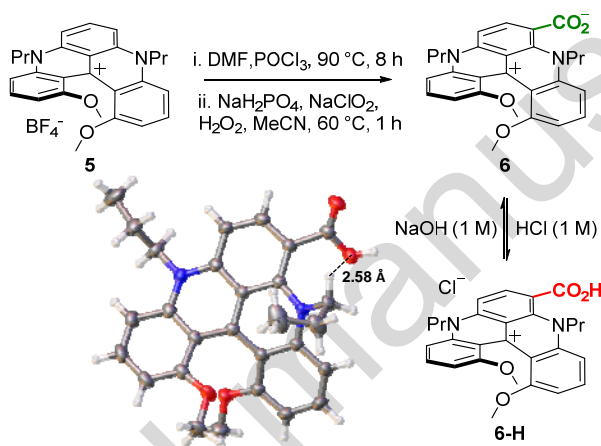

Figure 2. Synthetic route to **6/6-H** from diaza [4]helicene **5** and anisotropic displacement ellipsoids plot at 50 percent probability level of the crystal structure of **6-H**. Only *P* enantiomers are shown and trifluoroacetate anion is omitted for clarity from the structure.

Care was taken for this study to perform the reaction not only with *rac*-**5** but also with separated *M* and *P* enantiomers. The product is isolated as zwitterionic dye **6** and it undergoes color change in solution from green to purple upon acidification of the medium, corresponding to the conversion to the protonated carboxylic acid **6-H**. Single crystals of *rac*-**6-H** suitable for crystallographic analysis were obtained by slow evaporation (one month) of the compound in a mixture of methanol and water in presence of trifluoroacetic acid. The solid state structure of the trifluoroacetate salt of **6-H** reveals a folding of one *n*-propyl side-chain due to the establishment of an intramolecular CH···O interaction between the terminal O atom of the carboxylic acid and one hydrogen atom of the propyl chain (NC*H$_2$* fragment, Figure 2). This [4]helicene displays a helical pitch of 3.23 Å between the two carbon atoms bearing the methoxy groups and a helical angle of 42.8°, these values being sensibly higher than those measured for the parent compound **5** but comparable to analogous diaza [4]helicenes presenting intramolecular H interactions.[10]

With **6** in hand, the water solubility of this acid-base pair was investigated by screening the absorption variations in function of the concentration in acidic or basic aqueous solutions. The results are reported in Figures S1 and S2. No significant variation of the molar extinction coefficients (ε) were recorded below concentrations of 10^{-4} M and 4.10^{-4} M, allowing to estimate that the solubility is maintained up to 100 mg.L^{-1} and 400 mg.L^{-1} for **6-H** and **6** respectively, the deprotonated species being as expected more soluble due to its zwitterionic character.[11] Following these results, using a concentration of 10^{-5} M for **6**, a pK$_a$ of 2.9 was determined by screening the absorbance at 630 nm in a wide range of acidic and basic aqueous solutions (Figure 3). This value demonstrates a rather high acidity for **6-H** compared to simple

references such as *p*-amino- or *p*-nitro-benzoic acids (pK$_a$ ~ 4.9 and 3.4 respectively).[12] This might be the result of the intramolecular CH⋯O interaction that ought to stabilize carboxylate **6**, even more than **6-H**.

The pH-dependent absorption and fluorescence spectra of **6/6-H** in water are presented in Figure 3 and the relevant optical data are compiled in Table 1 (see Figure S3 for absorption and
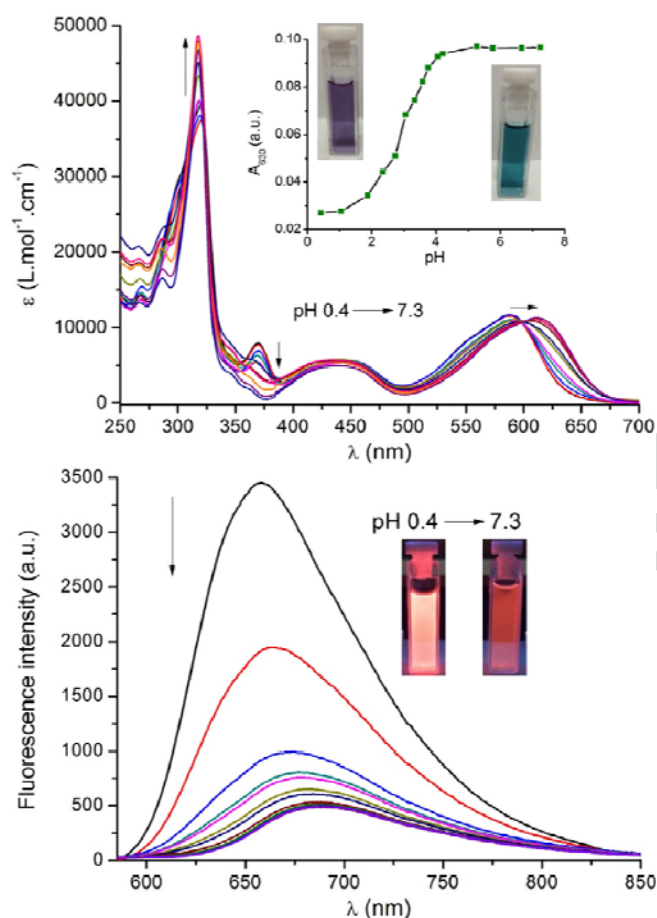

Figure 3. pH-dependent absorption and fluorescence spectra of **6/6-H** in aqueous solution (*ca.* 10^{-5} M). Insert: Optical density measured at 630 nm in function of the pH for **6/6-H** in aqueous solution.

fluorescence in acetonitrile). In its carboxylic form, compound **6-H** displays an absorption band centered at 587 nm, with a profile comparable to its parent unsubstituted diaza [4]helicene **5**, *i.e.*, an intense and relatively sharp lower energy transition exhibiting a shoulder at *ca.* 550 nm.[7a, 8b] With increasing pH, the lower energy transition is broadened and red-shifted to 612 nm. Such bathochromic shift can be ascribed to the establishment of an intramolecular charge transfer (ICT) from the anionic carboxylate function towards the cationic helicene scaffold, as demonstrated by the theoretical investigations (*vide infra*). The protonated species **6-H** presents fluorescence maxima at 675 and 654 nm in aqueous and acetonitrile solutions characterized

Table 1. Optical properties in acetonitrile and water.

Dye	solvent[a]	λ$_{max}$ / nm (ε$_{max}$ / L.mol^{-1}.cm^{-1})	λ$_{em}$ / nm	Φ[b]	τ$_1$ / ns[c]	τ$_2$ / ns[c]
6	CH$_3$CN	626 (10400)	709	0.01	0.8 (0.53)	3.5 (0.47)
6	H$_2$O	612 (11300)	690	0.02	1.3	-
6-H	CH$_3$CN	590 (11300)	654	0.29	13.0	-
6-H	H$_2$O	587 (11700)	675	0.10	4.3 (0.87)	10.5 (0.13)

[a] In CH$_3$CN in presence of HBF$_4$ or Et$_3$N; in H$_2$O in presence of HCl or NaOH. [b] Relative to Cresyl Violet (Φ = 0.54 in MeOH); estimated error = ± 10%. [c] NanoLED excitation at 570 nm, composition is indicated in parentheses.
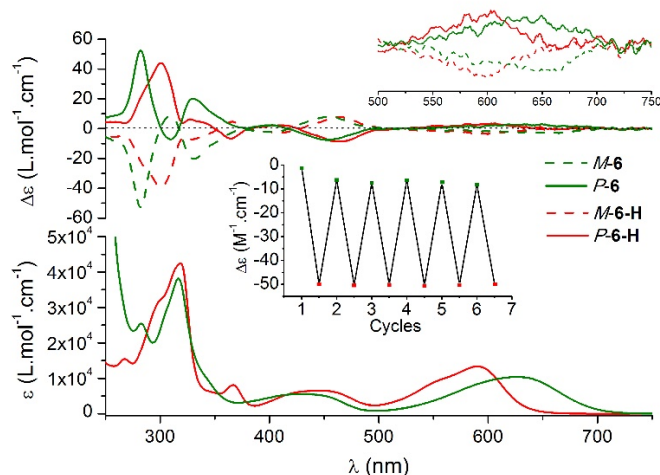
Figure 4. Top: ECD spectra (ca. 10^{-5} M) of *M*-**6-H**, *P*-**6-H** (CH_3CN + HBF_4) and *M*-**6**, *P*-**6** (CH_3CN + Et_3N). Bottom: absorption spectra of *rac*-**6-H** (red) and *rac*-**6** (green) in CH_3CN, added for comparison. Insert: reversibility of pH-switching monitored at 300 nm for *M*-**6/6-H**.

by quantum efficiencies of 0.29 and 0.10 respectively. The luminescence of zwitterion **6** is sensibly red-shifted compared to the protonated species and nearly quenched with a fluorescence quantum yield approaching 0.01 ($\Delta\lambda_{em}$ = 55 and 15 nm in acetonitrile and water respectively). This dramatic loss of fluorescence intensity is particularly attractive for the design of a turn-on CPL probe (*vide infra*). As previously observed for compounds of type **5**,[7a] the fluorescence lifetimes measured for zwitterion **6** in acetonitrile and cation **6-H** in water revealed two emissive contributions which can then be attributed to solvated and aggregated forms of the dyes in the corresponding solutions.

The UV-Vis electronic circular dichroism spectra of enantiopure *M*- and *P*-**6/6-H**, recorded in acidic or basic acetonitrile solutions, are presented in Figure 4 and the ECD spectra in aqueous solution are provided in Figure S4. In the UV region, **6** and **6-H** present maxima centered at 280 and 300 nm respectively, characterized by molar circular dichroism values ($\Delta\varepsilon$) of 40-50 $M^{-1}.cm^{-1}$. As expected,[10, 13] Cotton effects are moreover observed for both species in the blue (460 nm) and red (600-650 nm) spectral ranges.
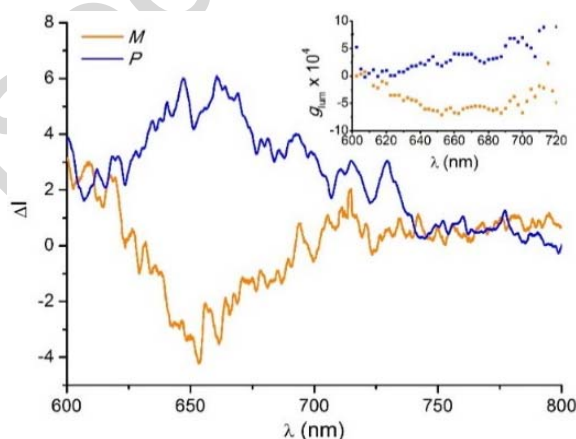

Figure 5. CPL spectra and g_{lum} response (insert) of the two enantiomers of **6-H** in acidic acetonitrile solution (HBF_4 1 M).
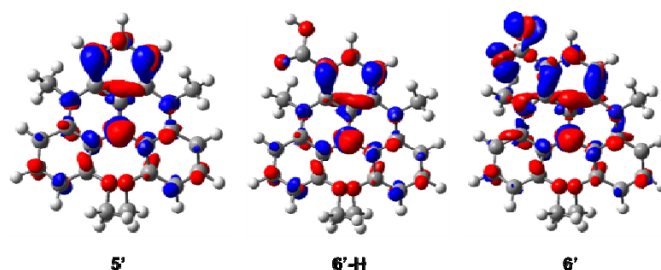
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Figure 6. Density difference plots for the first excited state of diaza [4]helicenes **5'**, **6'-H** and **6'**. The red (blue) zones indicate increase (decrease) of density upon lowest electronic transition (contour threshold 0.002 au).

Advantageously, while the cationic species **6-H** presents an ECD maximum at 300 nm, no response is measured for the deprotonated form **6** at this wavelength, allowing a convenient ON/OFF switching of the circular dichroism in the UV region with an amplitude of 50 $M^{-1}.cm^{-1}$. To a lesser extent, such phenomenon is observed at 352 nm and in the red range at 660 nm, where ECD is only recorded for zwitterion **6** ($\Delta\varepsilon$ ~ 10 and 2.5 $M^{-1}.cm^{-1}$). The robustness of ECD switching from *M*-**6** to *M*-**6-H** was assessed over six protonation-deprotonation cycles by addition of concentrated HBF_4 or Et_3N aliquots, demonstrating quantitative and reversible switching (Figure 4 and Figure S5).[14]

Enantiomers *P*-(+) and *M*-(−) of **6-H** in acidic acetonitrile solution (HBF_4 1 M) display weak monosignate CPL signals with a maximum at ~650 nm (Figure 5), as expected from the fluorescence spectra. The signs of the bands for the two enantiomers are in agreement with the sign of the most red-shifted Cotton effect, *i.e.*, the bands centered at 600 nm in the ECD spectrum (Figure 4). The g_{lum} factor, defined as $2\Delta I/I$, is estimated to 5.10^{-4} in water and acetonitrile, however since the compounds are much more emissive in acetonitrile, the CPL spectra display a higher S/N ratio (see Figure S6 for CPL spectra in water). These values are very similar to the absorption dissymmetry factors at 600 nm estimated from the CD spectrum ($g_{abs} = 4.10^{-4}$). This indicates that there is no significant geometry change between the ground electronic state and the emitting excited state. Moreover, the measured g_{lum} factors are in agreement with those previously reported for organic compounds.[10, 15] The narrow range of concentration investigated ($1-5.10^{-5}$ M) did not appear to change significantly the normalized intensities of the spectra. Owing to insufficient emission in basic medium, it was not possible to record any significant CPL signal for zwitterion **6**, thus validating the ON/OFF CPL switching between the two species.

Finally, a modelling of the electronic properties was undertaken *in silico*. For simplicity, the propyl side-chains were replaced by methyl groups and calculations were performed on compounds **5'**, **6'-H** and **6'** corresponding to the truncated derivatives. The delta density plots ($\Delta\rho$) of diaza [4]helicenes **5'**, **6'-H** and **6'** are displayed in Figure 6 whereas the computed and measured positions for the first band are compared in Table S2 (frontier orbitals are also shown in Figure S7). In the case of cation **5'**, the central carbon atom(s) is a node in the HOMO but not in the LUMO. One clearly notices that the HOMO, LUMO (Figure S7) and $\Delta\rho$ plots are delocalized on the whole structure. The charge on the central carbon atom of **5'** is + 0.16 *e* in the ground-state and − 0.03 *e* in the excited-state, undoubtedly showing that this central carbon atom is not the sole to bear the total positive charge, as the Lewis structures showed in Figure 2 could suggest. Clearly, the carboxylic acid functional group on **6'-H** has a small impact on the overall shapes of the frontier orbitals and density difference plots. In contrast, for the carboxylate species **6'**, ICT takes place from the substituents towards the fused ring system, explaining the red-shift of optical properties upon deprotonation. The computed ICT distance is very similar in **5'** (0.94 Å) and **6'-H** (0.90 Å), but is more than doubled in the carboxylate form **6'** (2.05 Å). As can be seen in the ESI (Figure S8), the theoretical ECD spectrum also matches the experimental one.

Conclusions

In summary, the investigation of the pH-dependent chiroptical properties of a readily accessible and water-soluble diaza [4]helicene revealed an efficient and reversible turn-on of ECD at selected wavelengths and of CPL in the red domain. Assuming that this latter spectral region is of first importance

for bio-imaging, we hope that such example will motivate the development of chiroptical switches as responsive probes for future use in imaging assays requiring chiral recognition.

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Graphical abstract