Modular Synthesis, Orthogonal Post-Functionalization, Absorption, and Chiroptical Properties of Cationic [6]Helicenes**

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Helicenes,^[1] which are *ortho*-condensed polyaromatic compounds, are omnipresent in chemistry, biochemistry, and physics as a result of their many different properties and applications.^[2] Of importance, these properties can be addressed by introducing substituents at the periphery of the helical cores or by changing the nature of the atoms within. From a synthetic standpoint, such modifications are not always trivial. Introduction of heteroatoms or postfunctionalization of helicenes with exocyclic substituents can be difficult to achieve selectively.^[3] For this reason, changes are usually made on building blocks prior to the completion of the helical skeletons. Herein, in an effort to overcome this limitation, we report a new class of cationic diaza-, azaoxo-, and dioxo[6]helicenes. The compounds **1–3** (Figure 1) are prepared in one step from a single common



Figure 1. The cationic diaza 1, azaoxo 2, and dioxo 3 [6]helicenes, and the [4]helicene quinacridinium derivatives of type 4. Only the *P* enantiomers are shown. R = alkyl chains.

advanced synthetic intermediate. Selective functionalization of **1** is readily achieved by series of orthogonal regioselective aromatic electrophilic and vicarious nucleophilic substitutions. Reduction, cross-coupling, or condensation reactions also introduce diversity. As a consequence, UV/Vis absorp-

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tion properties are easily tuneable up to the near-infrared region thanks to these late-stage transformations.

Previously, quinacridinium derivatives of type **4** have been reported (Figure 1). They are configurationally stable [4]helicenes (ΔG^{+} of racemization is ca. 42 kcalmol⁻¹) and very stable carbocations (p $K_{R+} \approx 19$).^[4] Quite a few applications of these compounds have been developed.^[5] None of them mention, however, a peripheral functionalization of the aromatic core. In fact, attempts to introduce substituents to **4** lead to mixtures of products because of the lack of chemical differentiation among the three benzo rings.^[6] It was thus decided to prepare other cationic heterohelicenes, which could be highly tuneable after their formation, such as the [6]helicenes **1–3**.

Access to these compounds was achieved using a modular route made of stepwise additions of the aromatic subunits and controlled sequential ring closures, as summarized in Scheme 1. The first step was the addition of (2,6-dimethoxyphen-1-yl)lithium to 2-methoxy-1-naphthaldehyde. The



Scheme 1. Reagents and reaction conditions: a) (2,6-dimethoxyphen-1-yl)lithium, Et₂O, 16 h, $-78 \rightarrow 25$ °C, 68%; b) DDQ, CH₂Cl₂, 20 h, 25 °C, 98%; c) BBr₃, CH₂Cl₂, 4 h, $-78 \rightarrow 25$ °C, 94%; d) neat, 2 h, 225 °C, 99%; e) (2-methoxynaphthalen-1-yl)lithium, CeCl₃, Et₂O,14 h, $-78 \rightarrow 25$ °C; f) HBF₄, 97% over 2 steps. DDQ=2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

resulting alcohol **5** (68%) was oxidized to the ketone **6** (98%, DDQ, CH_2Cl_2). Then, treatment with BBr₃ (1 equiv) regioselectively generated the phenol **7**, which underwent a clean O-ring closure upon heating at 225 °C (neat, combined yield 93% for the two steps). Reaction of the resulting tetracyclic ketone **8** with (2-methoxynaphthalen-1-yl)lithium in the presence of $CeCl_3^{[7,8]}$ then afforded, after work-up with HBF₄, [**9**][BF₄] in excellent yield (97%). The whole sequence is readily performed on multigram scale.

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Helicenes of type 1, 2, and 3 were then prepared using [9][BF₄] as single common precursor. The diaza derivatives 1a–d (Scheme 2) were synthesized by treatment of [9][BF₄] with the corresponding anhydrous aliphatic amines (25 equiv,



Scheme 2. Reagents and reaction conditions: a) Anhydrous RNH_2 (25 equiv), NMP, MW 170 °C, 10 min; b) PPh₃, DIAD, CH₃COSH, THF, 25 °C; c) *n*-PrNH₂, 49 °C, 30 min, then heated neat at 200 °C, 5 min; d) Pyr-HCl, 224 °C, 2 min then ion exchange metathesis with HBF₄. DIAD = diisopropyl azodicarboxylate, MW = microwave, NMP = *N*-methyl-2-pyrrolidone, THF = tetrahydrofuran.

NMP) and rapid heating under microwave irradiation (170 °C, 10 min).^[9] The resulting blue salts, **1a–d**, were isolated in moderate yields (43–47%). In the case of **1d**, facile transformation of the diol side chains into thioacetyl groups using Mitsunobu-type conditions was achieved to give **1e** (90%). To obtain the purple azaoxa salt **2a**, **9** was heated in neat anhydrous *n*-propylamine at reflux (49°C, 30 min). Then, after complete evaporation of the amine in vacuo at 20°C, application of a burst of heat (200°C, 5 min) afforded the mixed azaoxo derivative [**2a**][BF₄] in 40% yield. Finally, rapid treatment of [**9**][BF₄] in molten Pyr·HCl (224°C, 2 min) and ion-exchange metathesis (HBF₄, 25°C) afforded the red dioxo helicene **3** as its BF₄ salt in excellent yield (95%).

With these derivatives in hand, in particular salt [1a][BF₄], orthogonal routes to the selective functionalization of the helical core were developed. Electrophilic aromatic substitution reactions were first studied. A higher reactivity of the median phenyl ring over the flanking naphthyl subunits was predicted on account of the two donor nitrogen atoms attached to this ring (instead of one for the naphthyl groups). This assumption was rapidly confirmed. Treatment of [1a][BF₄] under nitration or halogenation reaction conditions (Scheme 3) afforded the corresponding dinitro 10, dichloro 11, and dibromo 12 derivatives in good to excellent yields (77, 97, and 96% respectively). A perfect regioselectivity was observed, wherein only positions 8 and 10 of the helical core, ortho/para to the two N atoms, reacted under these reaction conditions. Interestingly, with NIS, a milder monoiodination was obtained (13, 90%). Moreover, additional derivatizations were feasible with 10 and 12. For example, [10][BF₄] was readily reduced (H₂, cat. PtO₂) to the corresponding diamino derivative 14 (56%), and $[12][BF_4]$ was reacted under Suzuki-Miyaura and Sonogashira conditions to yield the corresponding diphenyl 15 (69%) and diphenylethynyl 16 (62%) derivatives.^[10]

Alternatively, taking into consideration the cationic character of the compounds **1** and the propensity of naphthyl



Scheme 3. Reagents and reaction conditions: a) HNO₃, 15 min, 25 °C; b) NCS (3 equiv), CHCl₃, AcOH, 15 h, 25 °C; c) NBS (3 equiv), CHCl₃, AcOH, 15 h, 25 °C; d) NIS (3 equiv), CHCl₃, AcOH, 15 h, 25 °C; e) H₂, PtO₂ (10 wt%), EtOH, 1 h, 25 °C; f) [Pd(PPh₃)₄] (10%), PhB(OH)₂ (5 equiv), K₂CO₃ (5 equiv), 1,4-dioxane, 15 h, 80 °C; g) [Pd(PPh₃)₄] (20%), Cul (30%), PhC=CH (10 equiv), Et₃N, 3 h, 90 °C. NBS = *N*-bromosuccinimide, NCS = *N*-chlorosuccinimide, NIS = *N*-iodosuccinimide.

rings to react with nucleophiles,^[11] [**1a**][BF₄] was treated with an excess of NaCN (3 equiv) in an open flask (Scheme 4).^[12] Full conversion was achieved but the resulting salt, [**17**][BF₄], bearing two nitrile groups at positions 5 and 13, was found to



Scheme 4. a) NaCN (3 equiv), DMF, 60 h, 25 °C; b) *n*-PrNH₂, 16 h, 25 °C; c) TMSN₃ (3 equiv), Bu₂SnO (20%), PhCl, 16 h, 60 °C. DMF = N,N-dimethylformamide, TMS = trimethylsilyl.

be sensitive to purification conditions (SiO₂, 17%). A similar reactivity was obtained in the treatment of [**12**][BF₄] with *n*-PrNH₂ (neat, 25°C) to afford the trisubstituted [**18**][BF₄] in good yield (74%). These vicarious nucleophilic substitutions afford, therefore, another means by which to modify the helical core under orthogonal (nucleophilic oxidative rather than electrophilic) conditions.^[13] Salt [**17**][BF₄] can be further transformed by reaction with trimethylsilyl azide to obtain the bis(tetrazole) analogue [**19**][BF₄] (60%).

Crystals of [12][BF₄] were grown by slow diffusion of Et₂O into a CH₂Cl₂ solution. Structural analysis by X-ray diffraction revealed, as expected, a helical conformation of the *ortho*-condensed framework (Figure 2).^[14] The compound 12 presents a larger helical pitch (3.31 Å) and angle (64.5°) between the two mean planes defined by the edge rings in

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2 **rr**



Figure 2. ORTEP view of the crystal structure of [**12**][BF₄]-CH₂Cl₂; *M* enantiomer shown. Thermal ellipsoids are drawn at 50% probability. Hydrogen atoms and solvent molecule are omitted for clarity.^[27]

comparison to those of the classical carbo[6]helicene^[2b,15] $(3.22 \text{ Å and } 58.5^{\circ} \text{ respectively}).^{[16]}$

As briefly mentioned, the novel salts [1a][BF₄], [2a][BF₄], and [3][BF₄] are colorful dyes and their electronic absorption spectra were recorded and are presented in Figure 3 (CH₂Cl₂, $2 \times 10^{-5} \text{ mol L}^{-1}$).^[17] All derivatives are characterized by moderately strong absorptions in the visible region $(13050 < \varepsilon < 16800 \text{ m}^{-1} \text{ cm}^{-1})$. The dioxo [3][BF₄] displays a maximum absorption band (λ_{max}) at 574 nm. No shift of this band is observed when one oxygen atom is replaced by a nitrogen atom.^[18] The presence of two nitrogen atoms causes, however, a moderate red shift of 45 nm ($\lambda_{max} =$ 619 nm).



Figure 3. UV/Vis spectra of a) [1a][BF₄] (blue), b) [2a][BF₄] (purple), and c) [3][BF₄] (red) recorded in CH_2Cl_2 (CH_2Cl_2 , 2×10^{-5} mol L^{-1}).

Of importance to the current study is a rather strong modulation of the visible absorption properties offered by the substituents introduced at the periphery of cation **1a**. Results are summarized in Table 1 and the corresponding spectra are displayed in the Supporting Information. When substituents are introduced on the upper phenyl ring (entries 1–7), the maximum absorption band varies from $\lambda_{max} = 567$ to 700 nm. Electron-withdrawing (EWG) and electron-donating (EDG) groups afford blue and red shifts, respectively. Interestingly, the opposite trend is observed when substitution occurs on the naphthyl rings (entries 8–10, $600 < \lambda_{max} < 690$ nm), with the lowest energy transition being that made by **17**, bearing

Table 1: Electronic properties: maximum absorption band (λ_{max}) and extinction coefficients (ϵ). CH₂Cl₂ solutions (2×10⁻⁵ mol L⁻¹).

Entry	Substituents	Compound	λ_{\max} [nm]	$\varepsilon \left[M^{-1} \mathrm{cm}^{-1} ight]$
1	8,10-NO ₂	10	567	18300
2	8,10-Cl ₂	11	620	13 000
3	8,10-Br ₂	12	620	13 000
4	8-1	13	620	13 000
5	8,10-C≡CPh	16	637	15 400
6	8,10-Ph	15	643	14 600
7	8,10-NH ₂	14	700	5100
8	5,13-tetrazole	19	620	17350
9	5,13-CN	17	690	17700
10	5-HN-nPr 8,10-Br ₂	18	600	30400

two cyano EWGs, and is in sharp contrast to the EDG-substituted **18** ($\lambda_{max} = 600 \text{ nm}$).^[19]

The enantiomeric resolution of 1a was also performed using the hexacoordinated phosphorus bis(tetrachlorobenzenediolato)-mono([1,1']binaphthalenyl-2,2'-diolato)phosphate(V) anion (BINPHAT; 20, Δ or Λ enantiomer; see the Supporting Information) as a resolving agent.^[20] The racemic salt $[1a][BF_4]$ and $[Me_2NH_2][\Lambda-20]$ (1.2 equiv) were mixed in a 1:1 mixture of CH₂Cl₂ and acetone. After concentration, NMR spectroscopic analysis (CDCl₃, 400 MHz) was performed and revealed an efficient enantiodifferentiation of 1a by anion 20.^[21,22] The crude mixture was dissolved in pure acetone and, upon cooling to 0°C, the formation of a precipitate was noticed. The blue solid was collected by filtration. The mother liquor was concentrated and ¹H NMR analysis (CDCl₃) indicated the presence of essentially one diastereomeric salt this time. Both fractions of the BINPHAT salts were converted into hexafluorophosphate salts by treatment with an excess of HPF₆ and KPF₆ in a mixture of CH₂Cl₂ and water. The salts (+)-[1a][PF₆] (e.r. 98:2) and (-)-[1a][PF₆] (e.r. 96:4) resulted from the mother liquor and solid fractions in 45% and 35% yields, respectively.^[23] Electronic circular dichroism (ECD) spectra (see the Supporting Information) displayed symmetrical curves in the $\lambda = 240$ to 700 nm region.

The absolute configuration of the helicene **1a** was then established by vibrational circular dichroism (VCD).^[24] IR absorption and VCD spectra were measured for solutions (CD₂Cl₂) of both (+)- and (-)-[**1a**][PF₆] and compared to the Boltzmann averaged spectrum calculated for (*P*)-**1a** (Figure 4) taking into account the most stable conformers found. Overall, a good agreement between the experimental and theoretical spectra is observed, thus allowing the assignment of *P* and *M* configurations for the carbenium ion in salts (+)- and (-)-[**1a**][PF₆], respectively.

Finally, the determination of the racemization barrier was attempted. DMSO solutions of (-)-[**1a**][PF₆] were heated at 180 °C and monitored in ECD at a single wavelength ($\lambda = 620 \text{ nm}$).^[25] No evidence could be found for a racemization after 5 hours of continuous heating. Performing the experiment at higher temperature (≥ 190 °C) in dibutyl sulfoxide failed as **1a** degraded in situ. As no racemization was observed after 5 hours at 180 °C, it is fair to say that **1a** presents a barrier of racemization of at least 37 kcal. mol⁻¹, which is within the range for that of [6]helicene.^[1,26]

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Figure 4. Experimental VCD spectra (CD_2Cl_2 , 298 K) of (-)-[1a][PF₆] (blue) and (+)-[1a][PF₆] (red). Calculated spectrum of (*P*)-1a (green).

Herein, we have thus presented novel cationic diaza-, azaoxo-, and dioxo[6]helicenes. These three classes of derivatives were prepared in one step from a common advanced intermediate. Straightforward, yet orthogonal, aromatic electrophilic and vicarious nucleophilic substitution reactions afforded a series of mono-, di-, and trisubstituted diazahelicenes which were additionally derivatized through crosscoupling, reduction, or condensation processes. The importance of this regioselective late-stage functionalization of the helical core was further evidenced in the strong modulation of the visible absorption properties of the cationic dyes. The diazahelicene can be resolved into single enantiomers, which demonstrates a high barrier to racemization.

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Helicenes

Communications

F. Torricelli, J. Bosson, C. Besnard, M. Chekini, T. Bürgi, J. Lacour* _____ IIII- IIII

Modular Synthesis, Orthogonal Post-Functionalization, Absorption, and Chiroptical Properties of Cationic [6]Helicenes



Pick and choose: Novel cationic diaza-, azaoxo-, and dioxo[6]helicenes are readily prepared and functionalized selectively by orthogonal aromatic electrophilic and vicarious nucleophilic substitutions (see scheme). Reductions, cross-coupling, or X = 0,0 RN,0 RN,NR

condensation reactions introduce additional diversity and allow tuning of the absorption properties up to the nearinfrared region. The diaza salts can be resolved into single enantiomers.

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