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Synthesis, Resolution, and Stabilities of a Cationic Chromenoxanthene [4]helicene

Joyram Guin,[†] Céline Besnard,[‡] and Jérôme Lacour*,[†]

Department of Organic Chemistry, University of Geneva, 30 Quai Ernest Ansermet, CH-1211 Geneva 4, Switzerland, and Laboratory of Crystallography, University of Geneva, quai Ernest Ansermet 24, CH-1211 Genève 4, Switzerland

jerome.lacour@unige.ch

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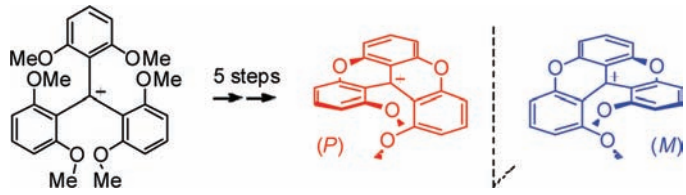
ABSTRACT



1,13-Dimethoxychromenoxanthenium, a key intermediate in the synthesis of the classical trioxatriangulenium cation, was isolated and characterized for the first time. This [4]helicene was resolved through a CSP-HPLC procedure, with chemical and configurational stabilities being determined and compared.

Trioxa- and triazatriangulenium ions $\mathbf{1}^+$ (TOTA$^+$) and $\mathbf{2}^+$ (Figure 1) are highly stabilized carbenium ions which can be obtained in only two steps from 1,3-dimethoxybenzene.[1] These compounds are formally triphenylmethylium ions rigidified and made planar by the bridging of all *ortho* positions of the aromatic rings by oxygen and nitrogen atoms (Figure 1).[2] Triangulenium ions and their derivatives have been intensely studied because of their large array of biological,[3] chemical,[4] photochemical/photophysical,[5] stereochemical,[6] structural,[7] supramolecular,[8] and synthetic[9] properties.

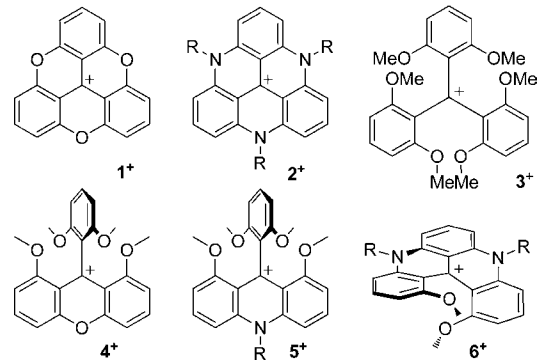


Figure 1. Trianguleniums $\mathbf{1}^+$ and $\mathbf{2}^+$, tris(2,6-dimethoxyphenyl)-methylium $\mathbf{3}^+$, and synthetic intermediates $\mathbf{4}^+$, $\mathbf{5}^+$, and $\mathbf{6}^+$ cations.

These derivatives are rather trivially prepared. Synthetic routes involve tris(2,6-dimethoxyphenyl)methylium ion $\mathbf{3}^+$ as precursor and successive *ortho* S_NAr reactions of oxygen and/or nitrogen nucleophiles. Some intermediates of one-ring or two-ring closure have been isolated: compounds

[†] Department of Organic Chemistry.
[‡] Laboratory of Crystallography.

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(2) Compounds **1** and **2** are 4,8,12-trioxadibenzo[*cd*,*mn*]pyrene and 4,8,12-trialkyl-8,12-dihydro-4*H*-benzo[1,8][2,7]naphthyridino[3,4,5,6-*klmn*]-acridine cations, respectively.

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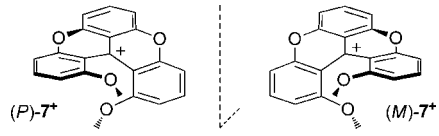
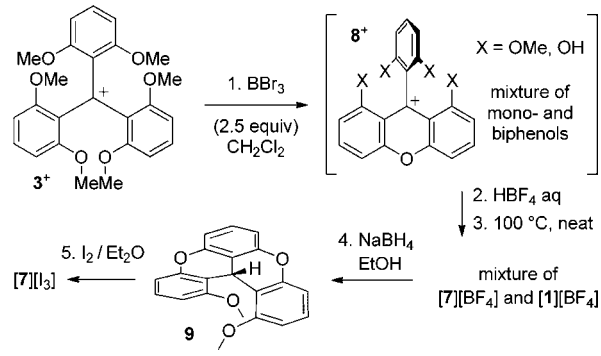


Figure 2. 1,13-Dimethoxychromenoxanthenium 7^+: *P* and *M* enantiomers.

4^+–6^+ (Figure 1).[4b,10] These compounds have interesting properties of their own. For instance, 5^+ is an effective photooxidant, and derivatives may present interesting conformations.[11] Quinacridinium 6^+ is a highly stable carbocation (pK_{R+} ~19) and one of the most configurationally stable helicenes.[1b,12] Compound 6^+ is also an interesting platform for the discovery of new reactivity and topology.[13]

However, surprisingly, there was no mention in the literature of 1,13-dimethoxychromenoxanthenium 7^+, the intermediate of two-rings closure in the oxo series (Figure 2). We wondered about the origin of this omission that could have come from a poor chemical stability of 7^+ and a natural tendency to form the trioxatriangulenium ion 1^+. It was debatable whether 7^+ could be made and observed. Herein, we report that cation 7^+ can indeed be isolated. It adopts a helical conformation as evidenced by NMR spectroscopy in the presence of a NMR chiral solvating agent and the characterization of its levo- and dextrorotatory enantiomers. However, contrary to its diaza analogue 6^+,[12] it presents rather low kinetic barriers to enantiomerization and ring closure.

Scheme 1. Synthetic Route to Cation 7^+



As discussed, the synthesis of triangulenium ions usually starts from a salt of cation 3^+. In the TOTA$^+$ series, demethylating conditions are used. For instance, salt [**3**][BF_4] is heated at 205 °C in the presence of pyridinium chloride, and in situ generated phenol moieties react in the *ortho* positions of the adjacent aromatic rings to form the desired planar cation.[1] Milder conditions have been reported (concd HCl, 100 °C followed SO_2Cl_2) which allow the clean synthesis and isolation of 4^+ as its chloride salt.[10] However, no report in these publications was made of the isolation of the second intermediate toward TOTA$^+$, chromenoxanthene 7^+.

However, our analysis determined that the demethylation of cation 3^+ should be better controlled. The dealkylating procedure should be selective and afford the deprotection of only two (out of six) methoxy groups. This would generate two phenolic moieties that ought to react intramolecularly to form 7^+ through (only) two *ortho* S_NAr reactions.

Such a selective deprotection turned out to be difficult. After a rather extensive search, it was found that the treatment of salt [**3**][BF_4] with 2.5 equiv of BBr_3 (CH_2Cl_2, 0 to 20 °C) afforded what we were essentially looking for in the form of a mixture of mono- and bisphenolic xanthenes 8^+ (Scheme 1).[14] After anion-exchange metathesis with aqueous HBF_4 and upon heating the resulting salts neat at 100 °C, the formation of desired [**7**][BF_4] was afforded along with major amounts of [**1**][BF_4]. Clearly, the formation of compounds 8^+ at 20 °C indicates that the first ring closure occurs spontaneously upon removal of the first methyl group in CH_2Cl_2. The second closure is more difficult and can only be achieved upon thermal activation. Salts [**7**][BF_4] and [**1**][BF_4] come then probably from the mono- and bisphenolic derivatives of 8^+, respectively. Ratios between the two salts varied somewhat from one reaction to the next (1:2 to 1:2.8).

Trying to improve on this result, salt [**4**][BF_4] was prepared[10] in the hope that the direct use of an advanced

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(14) Intermediates of type 8^+ were identified by ESI-MS.

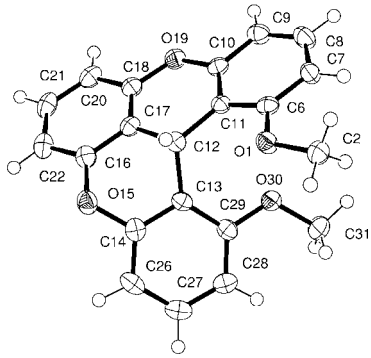

Figure 3. X-ray diffraction analysis of *rac*-**9**. Only the *M* enantiomer is shown.

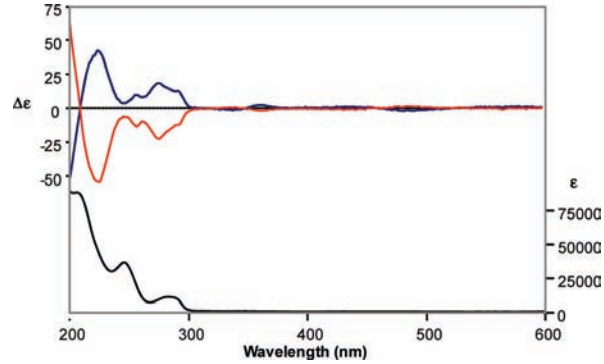

Figure 4. Electronic absorption spectrum of [**7**][I_3] (black, bottom) and ECD spectra (top) of (−)-[**7**][I_3] (red) and (+)-[**7**][I_3] (blue) in CH_3CN (5×10^{-6} M, 20 °C).

intermediate would help establish a cleaner deprotection protocol. Several conditions were tried (BCl_3 (3 equiv), 25 °C; aq HBr, water or acetone, 80 °C; NaI, DMF, 100 °C; BBr_3 (1 equiv), −78 °C). Unfortunately, either lack of reactivity, clean formation of $TOTA^+$, or even more complex mixtures of phenolic intermediates were afforded. The cleaner route to [**7**][BF_4] remained the one detailed above.

Clean separation of [**1**][BF_4] and [**7**][BF_4] could not be performed directly. Selective crystallization conditions were not found, and chromatography using polar eluents like MeOH failed due to the reactivity of these solvents with the electrophilic species. However, it is known that such cations react readily with hydride reagents to form neutral adducts,[7c] compounds that are usually easier to separate and purify than the original salts. As planned, treatment of the mixture of [**1**][BF_4] and [**7**][BF_4] with $NaBH_4$ (∼4 equiv, EtOH, 20 °C) afforded spontaneously a colorless solution of compounds that could be separated upon flash chromatography (SiO_2, Et_2O/pentane). Compound **9**, the reduced form of $\mathbf{7}^+$, was then isolated in 15% combined yield for the four steps from [**3**][BF_4]. It is highly crystalline.[15] An X-ray structural analysis was performed to confirm its chemical integrity (Figure 3). Finally, treatment of pure **9** with an excess of iodine in Et_2O afforded the corresponding [**7**][I_3] salt as a precipitate in quantitative yield. Its electronic absorption spectrum is reported in Figure 4.[16]

By analogy with dimethoxyquinacridinium ion $\mathbf{6}^+$, we considered that strong steric repulsions between the methoxy substituents in positions 1 and 13 of $\mathbf{7}^+$ should occur and prevent the cation from being planar. This derivative should thus adopt a twisted helical conformation typical of [4]helicene derivatives.[17,18] This assumption of stereochemistry was simply tested by the addition of [Bu_4N][Λ-BINPHAT] to a solution of [**7**][I_3].[12,19] This salt is an effective NMR chiral solvating agent for chiral cationic moieties.[20] Addition of 1.0 equiv of [Bu_4N][Λ-BINPHAT] to a $CDCl_3$ solution of [**7**][I_3] at room temperature led to an immediate split of some signals of $\mathbf{7}^+$, evidencing the existence of molecular chirality in the cation (see the Supporting Information). The signals for the methoxy protons are particularly well separated (δ 3.84 and 3.71 ppm, 400 MHz).

With this result in hand, we turned our attention to the resolution of $\mathbf{7}^+$. As for its separation from $\mathbf{1}^+$, we considered that the enantiomeric separation should be easier on the reduced compound **9** rather than on the charged moiety. Preparative chromatographic resolution on chiral stationary phases is now recognized as a very powerful and general method to separate and isolate enantiomers of racemic compounds in good yield and high optical purity.[21] This approach was applied to *rac*-**9**, and the two enantiomers were obtained on preparative scale using Chiralpak IB and a mixture of *n*-hexane/THF 99:1. From 20 mg of racemic **9**, after several runs, two separated fractions were afforded, 6 mg (ee > 99%, 30%) and 8 mg (ee 88%, 40%), for the first and second eluted fractions.[22] These fractions correspond to

(15) Monocrystals were already obtained in the collecting tubes of the chromatographic separation.

(16) For a comparison of the UV−vis and ^{13}C NMR spectra of $\mathbf{1}^+$, $\mathbf{3}^+$, $\mathbf{4}^+$, and $\mathbf{7}^+$ together, see the Supporting Information.

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(22) Retention times 12.1 and 13.3 min for these two fractions using an analytical Chiralpak IB (0.46 × 25 cm) and a mixture of *n*-hexane/2-propanol 99.2:0.8 as eluent. Flow 0.5 mL/min. UV 230 nm.

Table 1. Activation Parameters for Ring-Closure Reaction and Racemization of $\mathbf{7}^{+a}$

experiment	E_a[b]	A (s^{-1})	$\Delta H^{\ddagger}$ [b]	$\Delta S^{\ddagger}$[c,d]	$\Delta G^{\ddagger}$[b, d]
rac-$\mathbf{7}^+ \rightarrow \mathbf{1}^+$	32.2	4.9×10^{12}	31.6[d]	−2.4[d]	32.3[d]
(−)-$\mathbf{7}^+ \rightarrow$ *rac*-$\mathbf{7}^+$	24.5	2.8×10^{10}	24.0[e]	−12.7[e]	27.7

[a] Standard error values are reported in the Supporting Information. [b] kcal·mol^{-1}. [c] cal·K^{-1}·mol^{-1}. [d] At 20 °C.

(−)-**9** and (+)-**9**, respectively.[23] Upon oxidation (I_2 excess/Et_2O), the corresponding enantiomerically enriched carbenium salts (−)-[**7**][I_3] and (+)-[**7**][I_3] were afforded. Electronic circular dichroism (ECD) spectra display totally symmetrical curves in the 200 to 600 nm region. The spectra are reported in Figure 4.[24]

With racemic and enantioenriched salts in hand, the initial question of the determination of the kinetic barriers for (i) a spontaneous transformation of $\mathbf{7}^+$ into $\mathbf{1}^+$ and (ii) for the interconversion between the enantiomers of $\mathbf{7}^+$ could be examined. The natural tendency of $\mathbf{7}^+$ to form $TOTA^+$ was evaluated by ^{1}H NMR spectroscopy. Solutions of *rac*-[**7**][I_3] in DMSO-d_6 ($\sim 4 \times 10^{-3}$ M) were heated in the spectrometer. Formation of $\mathbf{1}^+$ was indeed observed, but it was necessary to bring samples to and above 120 °C.[25] Ratios between $\mathbf{7}^+$ and $\mathbf{1}^+$ were measured at timed intervals. Kinetic constants were calculated for the ring-closing process at four different temperatures (120, 130, 140, and 150 °C), and the determination of all activation parameters was realized (E_a, A, $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, and $\Delta G^{\ddagger}$, see the Supporting Information). The results are reported in Table 1. The value for the free energy of activation (32.3 ± 0.9 kcal·mol^{-1}) is in accordance with a rather low chemical stability of $\mathbf{7}^+$. The quasi-zero value for the entropy tends to indicate that this transformation involves an intramolecular process in the rate-determining step.[26]

The determination of the racemization barrier was performed by ECD, monitoring a single wavelength every second (277 nm, see the Supporting Information). It was necessary to heat DMSO solutions of (−)-[**7**][I_3] at 90 °C to start observing a decrease of the absorption. After 1000 s, only a 10% loss of enantiomeric purity was observed at that temperature. Samples were then heated at 90, 100, 110, and 120 °C and analyzed for the same period of time.[27] Kinetic constants were calculated and activation parameters determined. The results are reported in Table 1. Clearly, the racemization of $\mathbf{7}^+$ ($\Delta G^{\ddagger}$ 27.7 ± 0.4 kcal·mol^{-1}) occurs faster than the spontaneous transformation of $\mathbf{7}^+$ into $\mathbf{1}^+$. This rather large difference in kinetics indicates that the two processes evolve probably through distinct molecular pathways. To our surprise, this racemization of $\mathbf{7}^+$ is also much faster than that of $\mathbf{6}^+$ for which a rather high barrier was measured ($\Delta G^{\ddagger}$ 41.3 kcal·mol^{-1} at 200 °C).[12] Clearly, the two bridging oxygen atoms in the chromenoxanthenium skeleton bring a large degree of flexibility, contrary to the nitrogen atoms in $\mathbf{6}^+$.

In conclusion, 1,13-dimethoxychromenoxanthenium $\mathbf{7}^+$ was isolated and characterized for the first time. This cation is chiral, and its [4]helicene conformation was evidenced through a CSP-HPLC resolution. The configurational and chemical stabilities were then determined by CD and NMR spectroscopy and compared. Interestingly, the racemization of $\mathbf{7}^+$ is faster than the formation of the completely planar $TOTA^+$.

Acknowledgment. We are grateful for financial support of this work by the Swiss National Science Foundation and the State Secretariat for Education and Research.

Supporting Information Available: Synthesis and spectral characterization of *rac*-**9**, (+)-**9**, (−)-**9**, *rac*-[**7**][I_3], (−)-[**7**][I_3], and (+)-[**7**][I_3]. CSP-HPLC determination of the enantiomeric purity of **9**. Cyclic voltammogram and NMR enantiodifferentiation study of [*rac*-**7**][I_3]. Kinetic barrier measurements for (i) the ring-closure of *rac*-$\mathbf{7}^+$ to $\mathbf{1}^+$ and (ii) the racemization of (−)-$\mathbf{7}^+$ to *rac*-$\mathbf{7}^+$. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) Electronic circular dichroism (ECD) spectra of these two fractions display totally symmetrical curves in the 250−350 nm region. The spectra are reported in the Supporting Information.

(24) At the lowest energy, positive and negative Cotton effects ($\Delta\varepsilon_{483}$ = +1.4 and −2.4) are observed for the levo- and dextrorotatory salts, respectively .

(25) At 120 °C, the formation of $\mathbf{1}^+$ remains, nevertheless, very slow (half-life 26.6 h).

(26) This rate-determining step is most probably the nucleophilic attack of the oxygen atom from a terminal methoxy group onto the carbon that bears the other MeO group; subsequent demethylation (by attack of the solvent or by the leaving MeO^-) is then a faster process.

(27) At 120 °C, no measurable amount of $\mathbf{1}^+$ was observed after 1000 s in the ^{1}H NMR experiment performed in DMSO-d_6. We are thus confident of the reliability of the measurement of the kinetic constant of racemization at 120 °C.