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EDGE ARTICLE

[6]Saddlequat: a [6]helquat captured on its racemization pathway†

Louis Adriaenssens,^{‡a} Lukáš Severa,^{‡a} Dušan Koval,^a Ivana Císarová,^b Marta Martínez Belmonte,^c Eduardo C. Escudero-Adán,^c Pavlína Novotná,^d Petra Sázellová,^a Jan Vávra,^a Radek Pohl,^a David Šaman,^a Marie Urbanová,^e Václav Kašička^a and Filip Teplý^{*a}

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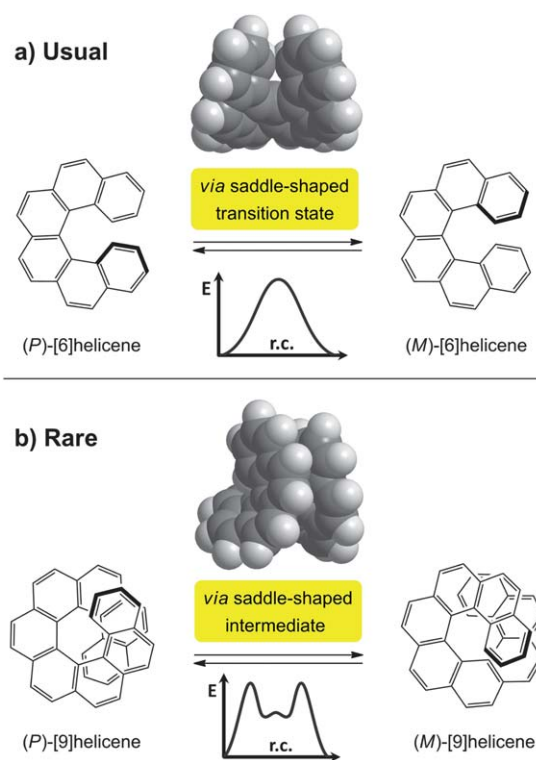
A dicationic [6]helicene congener captured on the racemization pathway in its saddle-shaped geometry is introduced. Synthesis, structure, resolution, and dynamic properties of this chiral [6]saddlequat in-between and its highly stereocontrolled transformation into enantiopure [6]helquat are discussed and demonstrated. The dynamic aspects established by experiment and supported by detailed DFT-D calculations are presented visually in the form of a movie (electronic table-of-contents and electronic supplementary information). The title [6]saddlequat was found to be an isolable chiral species on the entirely chiral enantiomerization pathway of a [6]helquat that is discussed as an example of Mislow's "rubber glove" molecule.

Introduction

Helicenes and helicene congeners continue to attract attention due to their fascinating helical shape, inherent chirality, and electronics.^{1–4} Because of their unique structure, their self-assembly,^{5,6} catalytic,⁷ chiroptical,⁸ and acid–base⁹ properties have been intensively studied. Furthermore, the recently reported ability of helicene congeners to inhibit the activity of telomerase,¹⁰ topoisomerase I,¹¹ and interact with DNA duplexes¹² and G quadruplexes¹³ promises interesting future applications.

A distinctive feature of helicenes is the existence of a thermal racemization pathway equilibrating the right-handed helix with the left-handed one ($P \rightleftharpoons M$, Scheme 1 and Scheme 2). This unique phenomenon of thermally triggered racemization *via* helix inversion has been extensively investigated.^{14–17} In a typical helicene, *e.g.* [6]helicene, helix inversion proceeds *via* a C_s -symmetric saddle-shaped transition state that is achiral

(Scheme 1a).¹⁶ In some rare cases, helicene congeners having saddle-shaped energy minima on their racemization pathways have been reported. Two examples, where the presence of such



Scheme 1 (a) Racemization of [6]helicene *via* achiral saddle-shaped transition state, (b) racemization of [9]helicene *via* saddle-shaped intermediate, and the corresponding energy profiles. r.c. = reaction coordinate.

^aInstitute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, v. v. i., Flemingovo nám. 2, Prague, 166 10, Czech Republic. E-mail: teplý@uochb.cas.cz; Fax: +420-220 183 578; Tel: +420-220 183 412

^bDepartment of Inorganic Chemistry, Charles University, Hlavova 2030, 128 40 Prague 2, Czech Republic

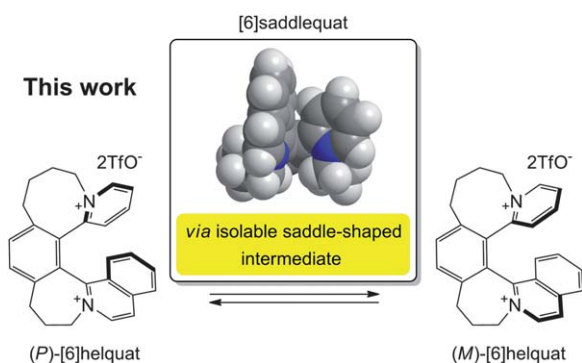
^cInstitute of Chemical Research of Catalonia (ICIQ), Av. Països Catalans 16, 43007 Tarragona, Spain

^dDepartment of Analytical Chemistry, Institute of Chemical Technology, Technická 5, Prague, 166 28, Czech Republic

^eDepartment of Physics and Measurements, Institute of Chemical Technology, Prague, Technická 5, Prague, 166 28, Czech Republic

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‡ These authors contributed equally to this work.



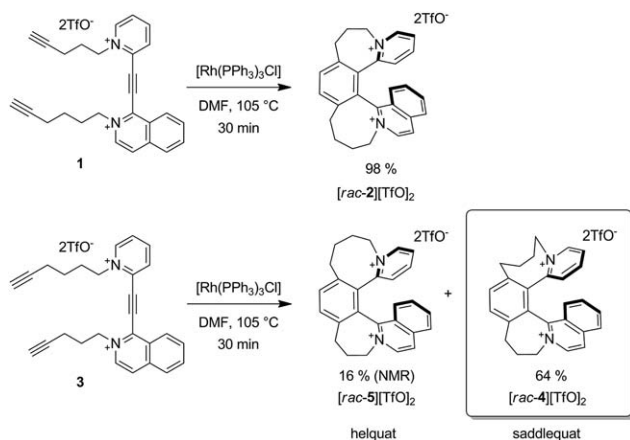
Scheme 2 Racemization of [6]helicene congener *via* isolable saddle-shaped intermediate studied in this work.

saddle-shaped energy minima is predicted, are [9]helicene (Scheme 1b)^{16b} and a recently disclosed [11]helicene derivative.^{17,18} We supposed, if the saddle-shaped energy minima existed in a sufficiently deep energy valley, then, the species corresponding to these minima could, in principle, be isolated and characterized as stable intermediates. They would represent a helical system captured during its racemization pathway.

Here we describe the synthesis, structure, and dynamic properties of a [6]helquat, a dicationic [6]helicene congener captured on the racemization pathway in its saddle-shaped geometry (Scheme 2). Resolution of this chiral saddle-shaped species and its highly stereocontrolled transformation into enantiopure [6]helquat is demonstrated.

Results and discussion

In our recent studies, we introduced helquats,^{19–22} helical dications that represent a missing structural link between helicenes and viologens. By taking advantage of a highly flexible three-step synthetic route,²¹ we accessed isomeric triynes **1** and **3** (Scheme 3 and ESI†). We found that, as usual, triyne **1** is transformed solely to the corresponding [6]helquat **2** *via* rhodium-catalyzed [2 + 2 + 2] cycloaddition.^{23,24} However, the isomeric triyne **3** leads under the same reaction conditions to formation of an isolable saddle-



Scheme 3 Triyne **1** leads solely to helical product **2** while isomeric triyne **3** gives the saddle-shaped species **4** as the major product.

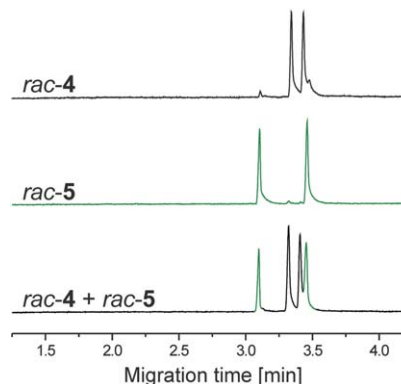
shaped species **4** along with the formation of [6]helquat **5**, featuring the typical helical shape. Both structures **4** and **5** were confirmed by a variety of spectroscopic methods.^{13C}, ^{1H}, HSQC, HMBC, COSY and ROESY NMR spectra permitted full assignment of all ^{1H} and ^{13C} resonances and established connectivity and spatial arrangement. Importantly, the three-dimensional identity of the individual dicationic frameworks has been unambiguously proved by single-crystal X-ray diffraction analyses (*vide infra*).²³

The saddle-shaped product **4**, which we suggest to denote as [6]saddlequat **4**, arises from a kinetically controlled [Rh(PPh₃)₃Cl]-catalyzed [2 + 2 + 2] cycloisomerization that furnishes a mixture of [6]saddlequat **4** and the corresponding [6]helquat **5** in a 4 : 1 ratio.²⁵ The solubilities of the diastereoisomeric salts [4][TfO]₂ and [5][TfO]₂ in tetrahydrofuran are considerably different and allow for the straightforward non-chromatographic separation of the two stereoisomers. Notably, and of particular importance for this study is that the saddle-shaped species [4] is sufficiently long-lived to be comfortably studied experimentally.

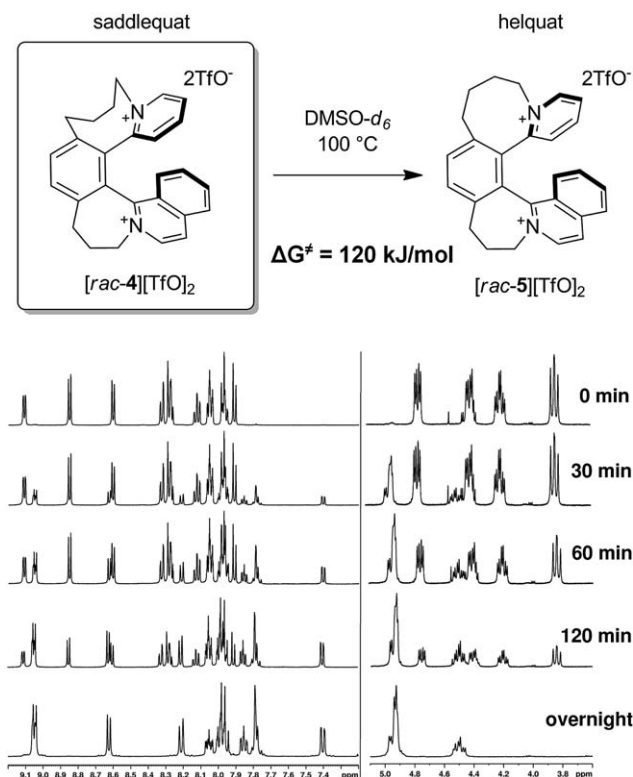
Moreover, both [5] and [4] are chiral entities formed as racemates during the [2 + 2 + 2] cycloaddition depicted in Scheme 3. This is evidenced by capillary electrophoresis (CE) with sulfated γ -cyclodextrin chiral selector, which shows two peaks of equal intensity corresponding to the two enantiomers of compound **4** (Scheme 4). A similar situation is observed in the case of compound **5**.^{26,27}

The calculated Gibbs free energy of the saddlequat [4] is 18 kJ mol⁻¹ higher relative to helquat [5] in DMSO as determined by DFT-D calculations²⁸ (TURBOMOLE:²⁹ B3LYP/def2-TZVP//ri-PBE/def2-SV(P) + disp³⁰ + DMSO,³¹ see ESI for details†³²). In line with this predicted energy difference, upon heating in DMSO-*d*₆ at 100 °C saddlequat [4][TfO]₂ gradually and completely converted to helquat [5][TfO]₂ (Scheme 5). This process can be followed by NMR *via* disappearance of peaks corresponding to [4] and appearance of peaks corresponding to [5] (Scheme 5). Data analysis from this experiment led to the activation free energy value ΔG^\ddagger of 120 kJ mol⁻¹ for the transformation [4] → [5].

In order to gain a thorough understanding of the conversion of [4] to [5] we turned to detailed DFT calculations. To this end,



Scheme 4 Saddlequat [4] and helquat [5] are both chiral entities. Both, [4] and [5], are produced from the triyne **3** in racemic form as evidenced by capillary electrophoresis with sulfated γ -cyclodextrin chiral selector.²⁷ See ESI for details.†



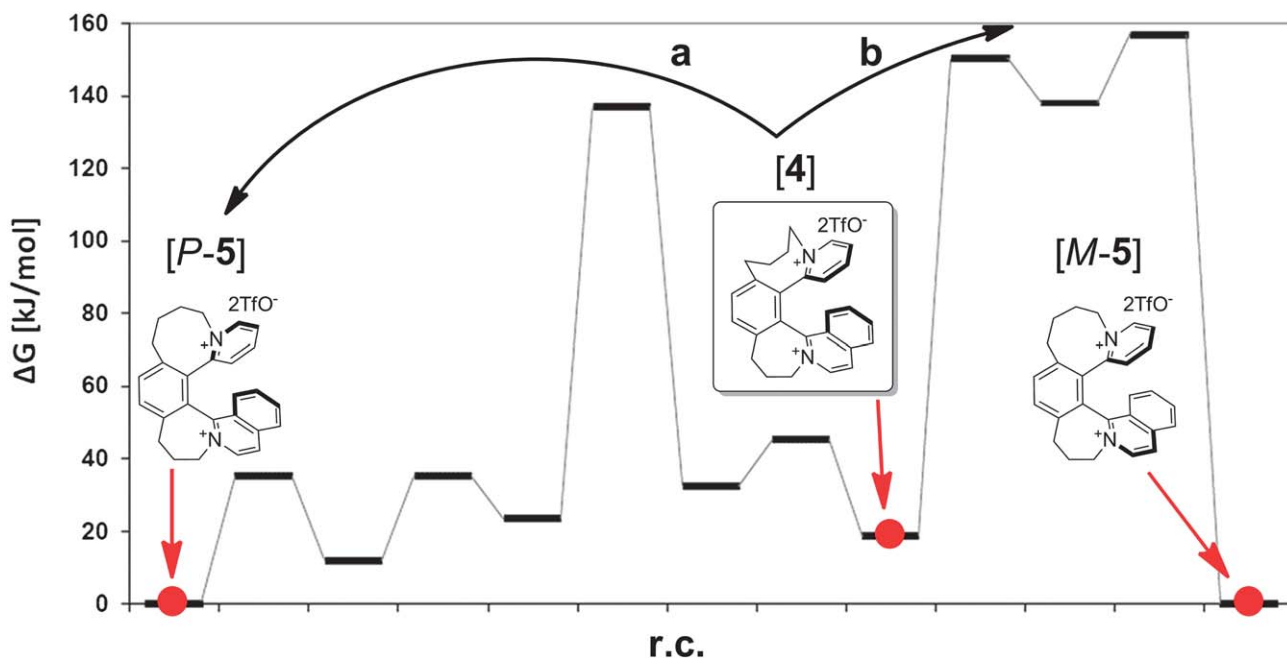
Scheme 5 Transformation $[rac-4] \rightarrow [rac-5]$ at 100 °C in $DMSO-d_6$ followed by 1H NMR.

TURBOMOLE calculations at the DFT-D level^{28–31} shed light on the energy profile of and structures involved in the entire racemization pathway of helquat [5] (Scheme 6). In line with our experimental results, calculation predicts that the saddlequat [4]

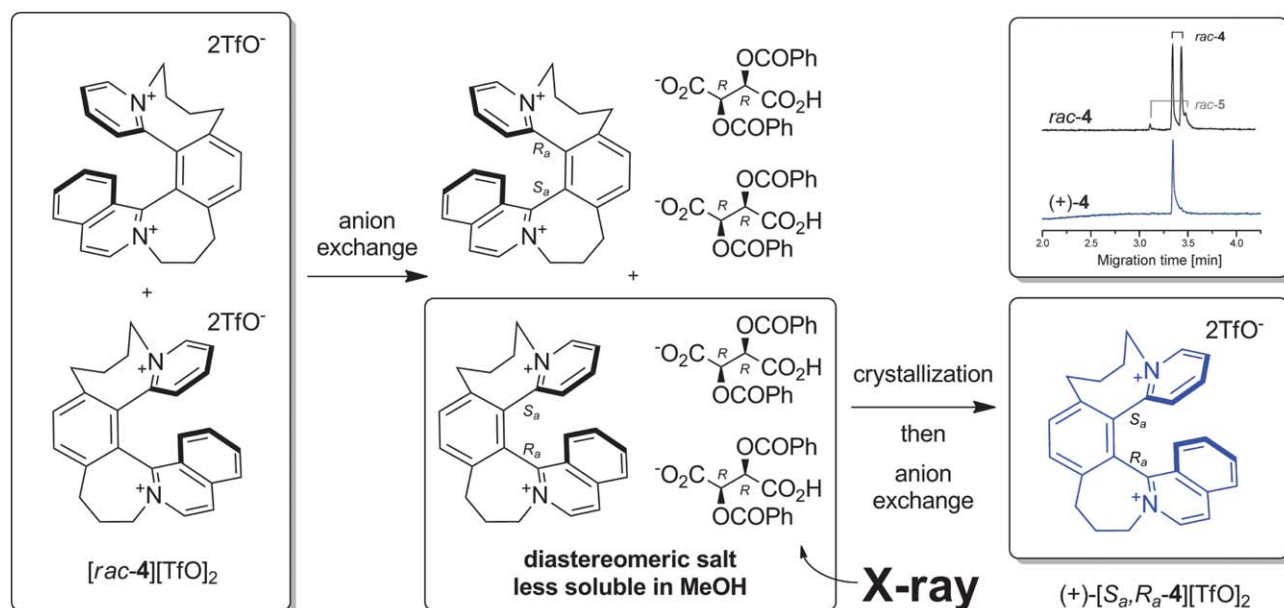
exists in this calculated energy profile as a local energy minimum that is in a sufficiently deep energy valley that it can be isolated and studied.

Inspection of the calculated energy profile around saddlequat [4] indicates that there are two possible, energetically distinct, pathways leading to two helquat [5] structures of opposite helicity (pathways a and b in Scheme 6). The lower, pathway a, corresponds to a ΔG^\ddagger value of 119 kJ mol⁻¹, which fits very well with the experimentally determined value of 120 kJ mol⁻¹ for transformation [4] \rightarrow [5] (see NMR study, Scheme 5). Following the energetically less favorable pathway b would also transform the same saddlequat to helquat, but now to the helquat of the opposite helicity.

We thus speculated that the existence of these two energetically distinct pathways would allow for the stereocontrolled transformation of enantiopure saddlequat [4] into enantiopure helquat [5] (via pathway a in Scheme 6). To test this hypothesis, access to non-racemic [4] was crucial. Therefore, we turned to resolution of racemic [4]. By employing the same resolution protocol recently reported for a [5]helquat derivative,^{20,33} we were able to achieve straightforward resolution of $[rac-4][TfO]_2$ (Scheme 7). Specifically, the exchange of triflate anions in $[rac-4][TfO]_2$ for enantiopure (*R,R*)-dibenzoyltartrate anions led to the formation of two diastereomeric salts, one of which crystallized from methanol in diastereomerically pure form, as evidenced by a single peak in the chiral CE trace.^{26,27} Single crystals suitable for X-ray diffraction analysis were obtained and enabled absolute configuration assignment of the dicationic scaffold of $[S_a,R_a-4]$ (Fig. 1).²³ Subsequent exchange of the (*R,R*)-dibenzoyltartrate anions in this diastereomerically pure salt for triflate anions via ion exchange resin completed the resolution giving (+)- $[S_a,R_a-4]$ ditriflate in its enantiomerically pure form (CE in Scheme 7).



Scheme 6 Calculated racemization pathway of helquat [5] passing through saddlequat [4]. Pathways a and b denote the two distinct routes from saddlequat [4] to the two enantiomeric helquats $[P-5]$ and $[M-5]$, respectively. See also the movie in the electronic table-of-contents and ESI for details.†



Scheme 7 Resolution procedure for $[rac-4][TfO]_2$ and the corresponding CE traces showing two peaks for $[rac-4]$ ditriflate and a single peak for the isolated $(+)-[S_a,R_a-4]$ ditriflate after resolution. See ESI for further details.†

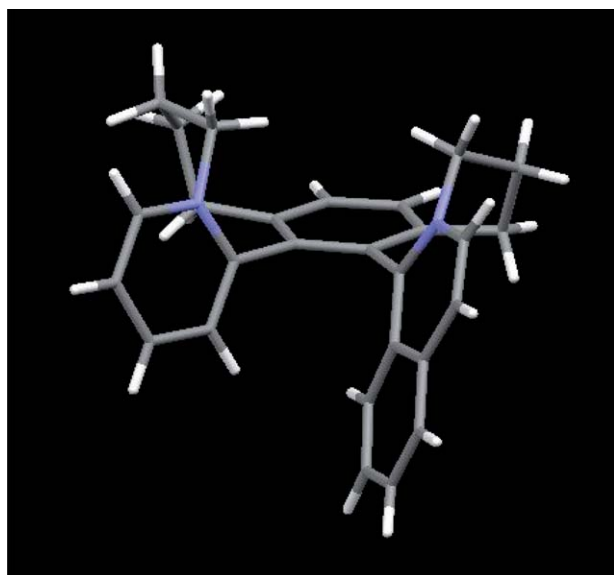


Fig. 1 X-Ray single crystal structure assigning absolute configuration of the dicationic framework of $(+)-[S_a,R_a-4][(R,R)\text{-dibenzoyltartrate}]_2$. (R,R) -Dibenzoyltartrate anions and crystal water molecules are omitted for clarity.²³

By heating this enantiopure sample of saddlequat $(+)-[S_a,R_a-4]$ ditriflate at $100\text{ }^\circ\text{C}$ in $\text{DMSO-}d_6$, we were able to confirm our hypothesis that the saddle-shaped species can indeed be transformed into enantiopure helquat **[5]** with no loss of chirality (Scheme 8). The experimental proof for this phenomenon was made possible by a powerful CE method using sulfated γ -cyclodextrin as a chiral selector.^{26,27} This provided us with an ideal experimental tool for monitoring the enantiocomposition of both **[4]** and **[5]** during the stereocontrolled transformation $[4] \rightarrow [5]$. CE electropherograms show a single peak

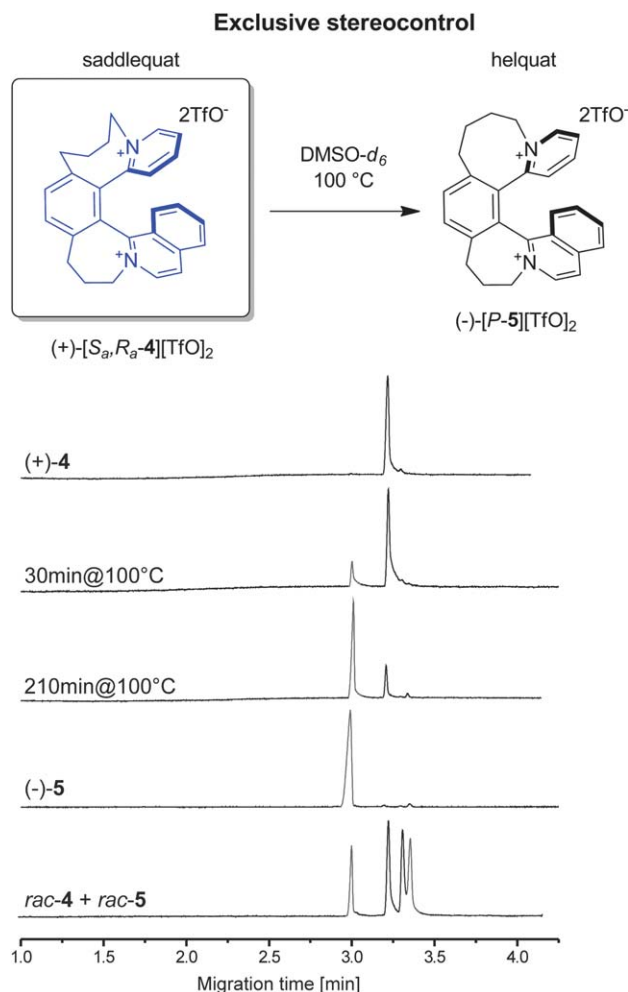
corresponding to the starting $(+)-[S_a,R_a-4]$ ditriflate giving rise to a single peak corresponding to $(-)-[5]$, providing definitive evidence for the complete stereocontrol governing this process (Scheme 8). The course of this stereocontrolled transformation $(+)-[S_a,R_a-4][TfO]_2 \rightarrow (-)-[5][TfO]_2$ was also followed by ECD spectroscopy. During the transformation, the characteristic peaks of $(+)-[S_a,R_a-4]$ ditriflate gradually give way to peaks of $(-)-[5]$ ditriflate positioned at longer wavelengths (Scheme 9).

To confirm that the saddlequat $(+)-[S_a,R_a-4][TfO]_2$ was transformed as predicted by calculation we sought the absolute configuration of the helquat $(-)-[5][TfO]_2$ formed during the process. Calculation predicted that in following the energetically more favorable pathway a, saddlequat $(+)-[S_a,R_a-4]$ would give rise to helquat **[5]** of *P* helicity (Scheme 6). Single-crystal X-ray diffraction analyses confirmed that this was indeed the case (Fig. 2).²³

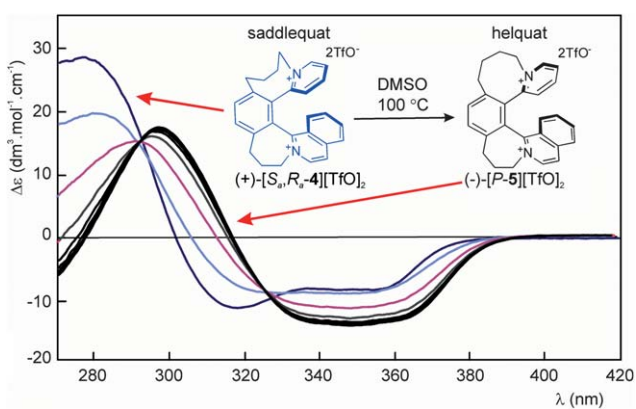
To evaluate the racemization barrier of helquat **[5]** it was essential to have a non-racemic sample of the compound. In our hands, stereocontrolled transformation of enantiopure $(+)-[S_a,R_a-4]$ proved to be the only feasible method to access enantiopure samples of helquat **[5]** as independent attempts at resolution of racemic **[5]** via diastereomeric salts failed.

With a route to enantiopure helix **5** established, a solution of $(-)-[P-5][TfO]_2$ in DMSO was heated at $180\text{ }^\circ\text{C}$. CE enantiocomposition analysis of samples taken over the course of heating determined the activation free energy value to be $\Delta G^\ddagger = 153.3\text{ kJ mol}^{-1}$ and the racemization half-life ($T_{1/2}$) to be 4.8 h at $180\text{ }^\circ\text{C}$. This experimentally determined racemization barrier fits well with that predicted by DFT-D calculations, ΔG^\ddagger of 157.7 kJ mol^{-1} (Scheme 10).

The consistent agreement between the experimental data and DFT-D calculations forms a body of evidence that can be best summarized in the dynamic visual form of the movie we present in the electronic table-of-contents.



Scheme 8 Chiral CE monitoring confirms complete stereocontrol in the transformation of saddlequat (+)-[*S_a,R_a*-4][TfO]₂ to helquat (-)-[*P*-5][TfO]₂ at 100 °C, as evidenced by the exclusive production of a single enantiomer of [5]. Bottom CE trace: reference mixture of [*rac*-4] and [*rac*-5]. See ESI for details.†



Scheme 9 ECD spectra recorded in the course of the stereocontrolled transformation (+)-[*S_a,R_a*-4][TfO]₂ → (-)-[*P*-5][TfO]₂ in DMSO at 100 °C. See ESI for further details.†

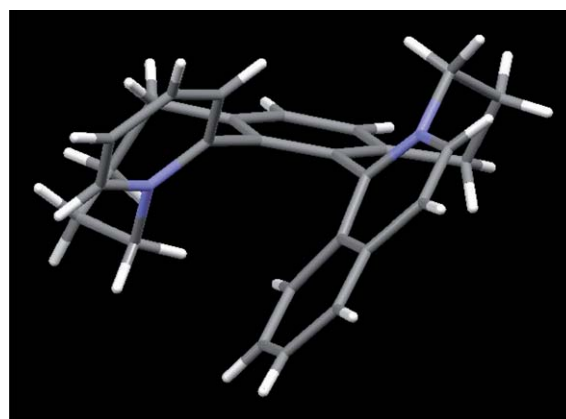
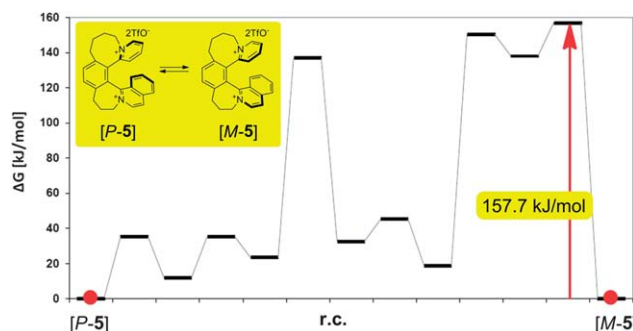


Fig. 2 X-Ray crystal structure assigning absolute configuration of helquat (-)-[*P*-5][TfO]₂ as obtained by stereocontrolled transformation from saddlequat (+)-[*S_a,R_a*-4][TfO]₂ at 100 °C. X-Ray quality crystals were grown from the perchlorate salt of [*P*-5]. Perchlorate anions and crystal water molecules are omitted for clarity.²³



Scheme 10 Thermal racemization of helquat [5][TfO]₂ proceeds at 180 °C in DMSO with $T_{1/2}$ of 4.8 h (experimental $\Delta G^\ddagger = 153.3$ kJ mol⁻¹, calculated $\Delta G^\ddagger = 157.7$ kJ mol⁻¹). See ESI for details.†

We note, that [6]helquat **5** represents an interesting example of a “rubber glove” molecule^{34,35} as its enantiomerization takes place exclusively by a chiral pathway *via* chiral [6]saddlequat **4**. As introduced by Mislow in the 1950s,³⁴ enantiomerization in “rubber glove” molecules can only proceed *via* chiral pathways as no achiral conformations can be attained for such structures. This molecular phenomenon is paralleled in the macroscopic world by turning a right-handed rubber glove inside-out leading to an object superimposable with a left handed-glove, never attaining an achiral (symmetric) conformation on its enantiomerization pathway.

Conclusions

In conclusion, we have presented a detailed experimental and theoretical investigation of a stereochemically rich³⁶ helicene-type racemization pathway featuring a saddle-shaped local energy minimum sufficiently stable to be isolated, characterized, and studied in detail. This saddle-shaped species arises from a kinetically controlled [Rh(PPh₃)₃Cl]-catalyzed [2 + 2 + 2] cycloisomerization of the triyne precursor.³⁷ Resolution of this chiral saddle species allows for production of enantiopure helix *via* a highly stereocontrolled chiral information transfer.³⁸

Capillary electrophoresis with sulfated γ -cyclodextrin chiral selector is shown as an advantageous and direct method for analysis of enantiocomposition of both saddle- as well as helical-shaped charged species. Finally, this study describes [6]helquat **5** as an example of a “rubber glove” molecule and introduces [6]saddlequat **4** as an isolable chiral species lying on the entirely chiral enantiomerization pathway of [6]helquat **5**.

Acknowledgements

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