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Mild and catalytic electrocyclizations of heptatrienyl anions†

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We report the synthesis of functionalized cycloheptanes by thermal electrocyclization of heptatrienyl anions under mild conditions. In addition, we disclose the first examples of this electrocyclization manifold conducted under catalytic conditions. Previously, electrocyclization of heptatrienyl systems required formation of anions with a strong base, resulting in limited functional group compatibility. We demonstrate that polarization of heptatrienyl anions using strategically positioned electron-withdrawing groups lowers the energy landscape of the reaction by stabilizing both the acyclic heptatrienyl anion and cycloheptadienyl product. Divergent reactivity is observed between aliphatic and aromatic substrates, with the latter requiring only catalytic amounts of base for complete conversion. This can be rationalized by the relative stability of the acyclic and cyclic anions and their ability to participate in a chain reaction process.

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1. Introduction

Ring construction is a priority task in the synthesis of value-added complex molecules. While the synthesis of small rings is routine, medium-sized rings are often difficult to access. Cycloheptanes are commonly found in drug candidates and complex naturally occurring compounds with biological activity of possible therapeutic value. Natural products bearing complex cycloheptanes have indeed served as drug leads or are drugs themselves, as exemplified by englerin,¹ and ingenol² (Fig. 1). A major challenge in their synthesis involves the preparation of a highly functionalized cycloheptane ring.

In the main, classical cycloheptane synthesis relies on the release of ring strain. For example, the de Mayo reaction³ and the divinyl cyclopropane rearrangement^{4,5} employ the release of ring strain from cyclobutane or cyclopropane intermediates respectively to drive cycloheptane synthesis.⁶ Another common approach involves one-carbon ring expansion of cyclohexanes, enabled by the Tiffeneau-Demjanov⁷ and pinacol-type rearrangements,⁸ or the ring expansion of cyclohexane-fused cyclopropanols.⁹ Besides ring-closing metathesis, other methods relying on transition metal catalysts have been developed, and they often feature high energy building blocks such as methylenecyclopropanes or vinylcyclopropanols.^{10,11}

Electrocyclization reactions are frequently used to make functionalized cyclopentanes^{12,13} and cyclohexanes. In contrast, although the electrocyclization of all-carbon heptatrienyl anions has been known for over fifty years, its use in synthesis remains very limited.¹⁴ Like other electrocyclizations, this process is thermodynamically driven largely by the formation of a strong sigma C–C bond at the expense of a weaker pi C=C bond. Early studies by Kleinschmidt, Kergomard, Klootzerziel and Bates^{15–18} relied on strongly basic conditions to generate heptatrienyl anions (eqn (1)). Sporadic studies of this electrocyclization manifold have appeared over the years,^{19–23} yet all reports involve strongly basic intermediates generated with a stoichiometric base, limiting the functional group tolerance and overall utility of this electrocyclization. We aim to transform this electrocyclization manifold into a more useful method for synthesis and in this report we detail our initial efforts towards this goal.

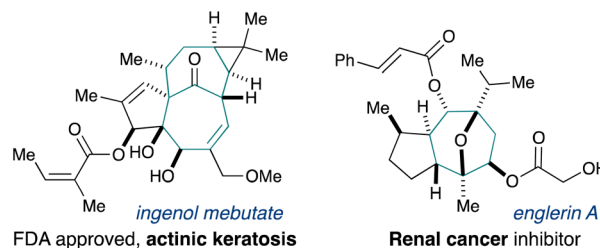
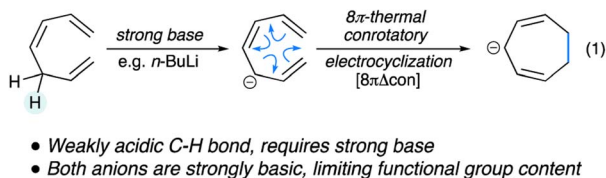


Fig. 1 Selected natural product drug leads bearing functionalized cycloheptanes.

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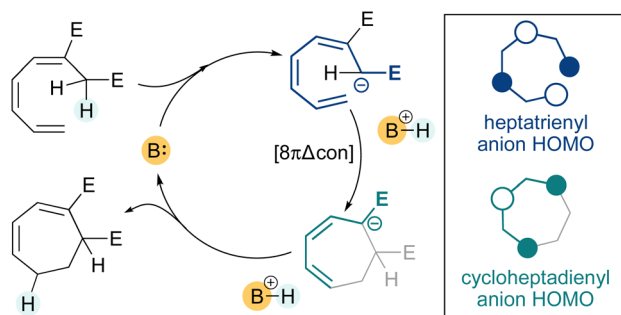
Original reports. Kleinschmidt, Kergomard, Klootzerziel, and Bates



2. Reaction design and development

Since electrocyclic cyclization is largely driven by the formation of a sigma bond, we reasoned that the basicity of the heptatrienyl and cycloheptadienyl anions should be largely irrelevant, provided they are similar (Fig. 2). Put differently, if both substrate and product anions were stabilized by strategically positioned and similar functional groups, the electrocyclic cyclization would remain thermodynamically favorable and would proceed under significantly milder conditions. The location of charge-stabilizing groups in the substrates would be guided by the alternating charge localization in the HOMO of the acyclic substrate and cyclic product anions (see inset). Originally we envisioned that if the pKa profile of the substrate, product and base would be within a narrow range, this could perhaps enable a catalytic process in which the conjugate acid formed by deprotonation of the heptatriene could protonate the cycloheptadienyl anion resulting from electrocyclic cyclization. Incorporation of activating functional groups would have the added benefit of facilitating substrate synthesis and could be exploited in downstream reactions.

To begin our study, we prepared a model substrate from cyclopentanone using a Vilsmeier-Haack bromoformylation, a Suzuki coupling, and a Horner-Wadsworth-Emmons reaction (see ESI for details†). This route provides substrates that are pre-organized for electrocyclic cyclization and that bear adjacent and nearly identical activating groups. The triene derived from cyclopentanone in this way (**S1**) was treated with various bases to promote the electrocyclic cyclization. Use of an excess of



- Heptatrienyl and cycloheptadienyl anion HOMOs are delocalized on alternating atoms, dictating the position of activating groups (E)
- Activated C-H bond, requires mild base
- Potentially catalytic process
- Both anions are weakly basic, tolerate functional groups

Fig. 2 Design principles for the mild and catalytic electrocyclic cyclization of heptatrienes to cycloheptadienes.

Table 1 Optimization of the electrocyclic cyclization of aliphatic substrates

Change from optimal conditions		
1	1.1 equiv. TBAF in THF	59%
2	0.1 equiv. TBAF in THF (0.1 M)	6%
3	DCM instead of DMSO (0.1 M)	0%
4	MeCN instead of DMSO (0.1 M)	70%
5	0.1 instead of 1.0 M	80%
6	none	89%
7	0.1 equiv. DBU	5%

TBAF as the base in THF at ambient temperature provided the desired cycloheptadiene (**1**) in 59% yield (Table 1, entry 1), however no turnover was observed when TBAF was used in catalytic amounts (entry 2). We then used DBU as a soluble organic base in a variety of solvents. No reaction took place in DCM (entry 3), and a satisfactory 70% yield of the electrocyclic product was obtained in MeCN (entry 4). The yield improved to 80% upon changing to more polar DMSO (entry 5) and to 89% upon increasing the concentration to 1.0 M. Unfortunately, using 10 mol% of base provided only 5% yield of the product. Other amine bases tested failed to give the desired product.

Unexpectedly, we found that the intermediate β -bromoaldehydes prepared from other ketones (*i.e.*, cycloheptanone and cyclooctenone) were unstable and this limited access to substrates through our initial approach. The triene products were also unexpectedly unstable and this led us to investigate substrates bearing an embedded benzene ring. These benzotrienes can be accessed from the corresponding *ortho*-bromobenzaldehydes through a Suzuki coupling and a Horner-Wadsworth-Emmons reaction (See ESI for full details†). We note in passing that all known examples of electrocyclic cyclization of heptatrienes that incorporate at least one aromatic ring require strongly basic conditions.^{14,24–26} In contrast to the aliphatic substrate, the reaction of benzotriene **S3** using TBAF in THF at ambient temperature failed (Table 2, entry 1), however a 57% yield of benzocycloheptadiene **3** was obtained at elevated temperature (entry 2). Changing the solvent and base to DMSO and DBU provided a very satisfying 90% yield of isolated product (entry 3). Remarkably, the use of a catalytic amount of DBU under similar conditions provided 86% yield of product (entry 4), even at higher concentrations (entry 5). These are the mildest conditions ever reported for electrocyclic cyclization of heptatrienyl anions, and the first demonstration of catalysis for this electrocyclic manifold.

3. Substrate scope studies

Satisfied with the mild conditions established for this electrocyclic cyclization, we began substrate scope studies. The aliphatic



Table 2 Optimization of the electrocyclization of aliphatic substrates

Change from optimal conditions		
1	1.1 equiv. TBAF in THF (0.1 M)	0%
2	1.1 equiv. TBAF in THF (0.1 M), 60 °C	57%
3	1.1 equiv. DBU in DMSO (0.1 M)	90%
4	0.1 equiv. DBU in DMSO (0.1 M)	86%
5	none	86%

substrates we could prepare (Fig. 3, **1** and **2**) both cyclized in good or moderate yield but required a stoichiometric base. The parent aromatic compound (**3**) cyclizes in excellent yield with a catalytic amount of base, and these conditions translate to the chloro-, trifluoromethyl- and fluoro-substituted substrates (**4**–**6**). The methoxy-substituted substrate (**7**) required a stoichiometric base and heating to give a satisfactory yield. This is perhaps not surprising because the methoxy-substituent is electron-donating by resonance, in contrast to all previous entries. Substrates bearing alkyl (**8**) or aryl groups (**9** and **10**) on the vinyl fragment also required excess base to reach completion and provided inseparable mixtures of diastereomers. These mixtures likely reflect the thermodynamic position, resulting from equilibration of the stereogenic center alpha to the ester group under reaction conditions, and should not be interpreted as representative of the anion geometry prior to electrocyclization. We prepared geometric isomers of the substrate bearing a nitrile group to stabilize the cyclized product and found that the *E*-isomer cyclized readily to **11**, however the *Z*-isomer (**S12**) did not cyclize under a variety of conditions, which suggests that the alkene bearing the nitrile cannot isomerize to adopt the necessary helical geometry prior to electrocyclization. Attempts to make the complementary compound to nitrile **11**, with the nitrile and ester groups switched (not shown), failed due to instability of the Horner–Wadsworth–Emmons reagent, which is prone to decomposition by elimination of the cyanide anion. A substrate bearing a terminal ketone group cyclized to give product **13** in 30% yield using 10 mol% DBU and marginally better yield using a stoichiometric base. The complementary substrate with the ketone and ester groups switched (not shown) could not be prepared due to low nucleophilicity of the Horner–Wadsworth–Emmons reagent. Finally, two substrates bearing a pyridine backbone rather than a benzene backbone (**14** and **15**) both underwent cyclization. These last two examples demonstrate nicely the subtle aspects of this electrocyclization. In the case of **14**, the charge in the electrocyclized anion is not resonance-stabilized by the imine-like moiety embedded in the pyridine and, as a result, is sufficiently basic to allow use of a catalytic base. In contrast, in the case of **15**, the charge in the electrocyclized anion is directly stabilized by the imine-like moiety in the pyridine, making it insufficiently basic to

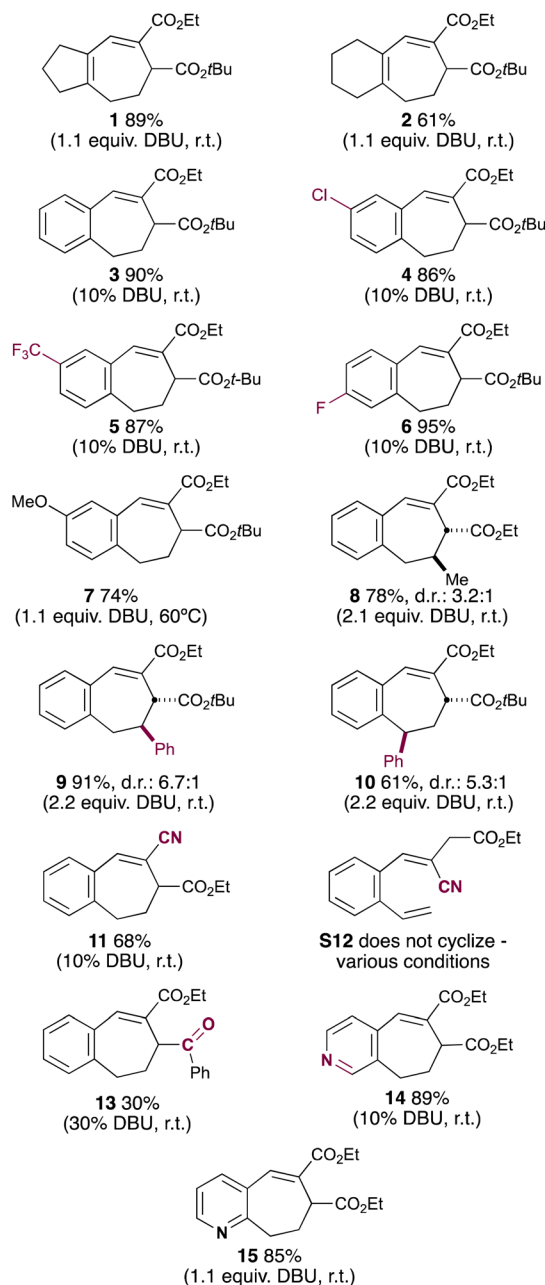


Fig. 3 Substrate scope of the electrocyclization of heptatrienyl systems.

deprotonate the conjugate acid of the catalytic base or the acyclic heptatriene substrate.

4. Theoretical and mechanistic studies

To gain some understanding of this electrocyclization reaction we conducted a theoretical study with a simpler model system, using amidine as the base and implicit DMSO solvent (Fig. 4).²⁷ The reaction begins with deprotonation of the acidic position with amidine base (**R** to **INT₁**) via transition state **TSC₁**·**H**·**N**.

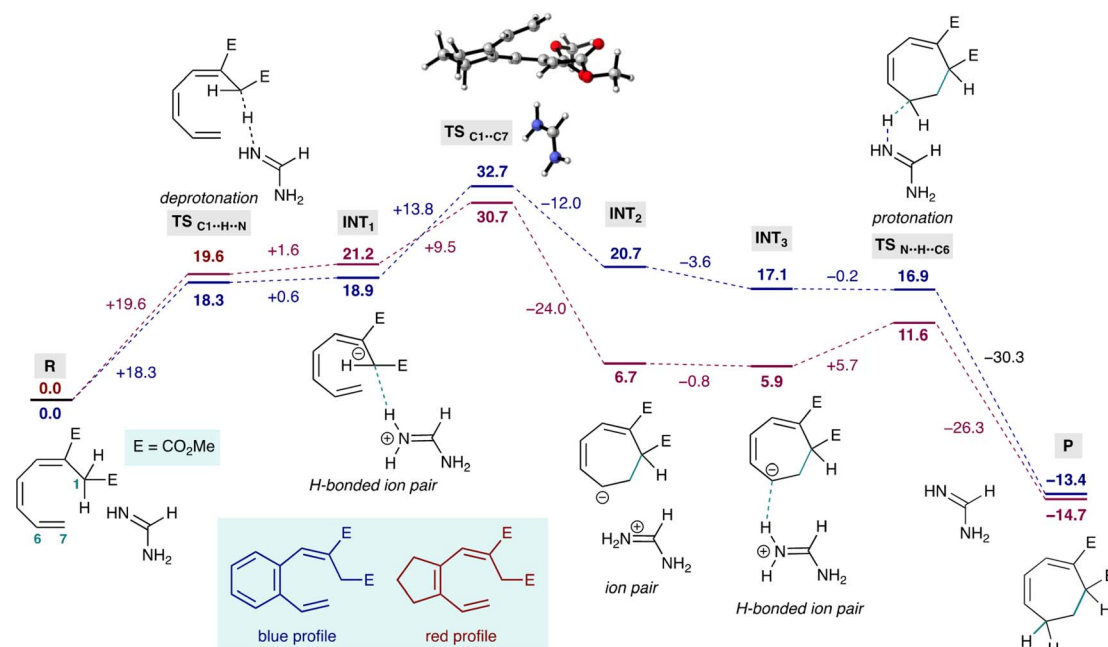


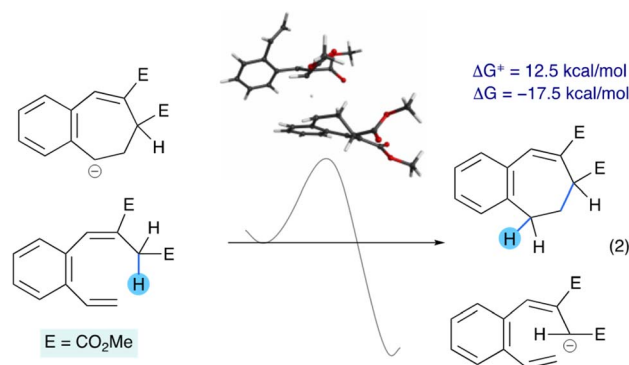
Fig. 4 Calculated reaction coordinate for electrocyclicization of heptatrienyl systems bearing a fused aromatic (blue) or aliphatic (red) ring, using amidine base and implicit DMSO solvent. The fused rings are omitted in the reaction profile for clarity. All energies are in kcal mol⁻¹.

INT₁ represents the helical anion hydrogen-bonded to the amidinium ion in DMSO solution. Electrocyclization ensues through transition state TS_{C1...C7} (the aliphatic TS is shown), which is hydrogen-bonded to the amidinium ion (H-bond omitted for clarity), yielding INT₂, the cycloheptadienyl anion as an ion pair with amidinium. Progression from INT₂ to INT₃ corresponds to the departure of the amidinium ion from C1 and approach of amidinium to C-6, forming INT₃, which has the same cycloheptadienyl anion as INT₂ but hydrogen bonded to amidinium. INT₃ leads to the final product through proton transfer via TS_{C...H...N}.

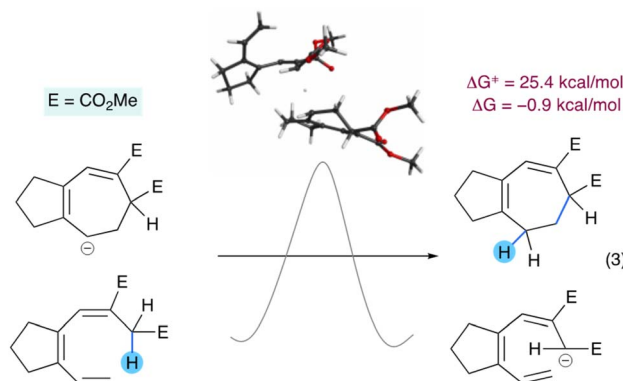
This study reveals that the electrocyclicization of the aliphatic system (red profile) is exergonic by -14.7 kcal mol⁻¹ and the electrocyclicization of the aromatic case (blue profile) is exergonic by -13.4 kcal mol⁻¹. This study also reveals that both electrocyclicizations have similar overall activation barriers (see ESI for computational results†), with the transition state for electrocyclicization occurring at 30.7 kcal mol⁻¹ for the aliphatic case, and 32.7 kcal mol⁻¹ for the aromatic case (Fig. 4). Interestingly, these calculations also suggest that the cyclized aromatic anion is less stable, and therefore more basic than the aliphatic counterpart (*c.f.* INT₂).

The relative energies of the acyclic and cyclic anions immediately before and after electrocyclicization (*c.f.* INT₁ and INT₂, Fig. 4) reveal that electrocyclicization of the aliphatic anion is favourable, and that the electrocyclicization of the aromatic anion is energetically uphill. This can be understood intuitively, considering that the aliphatic cycloheptadienyl anion benefits from stabilization by conjugation to the electron-withdrawing group at C2. While the same is true for the aromatic anion, this also involves perturbation of aromaticity, which is reflected in its higher energy.

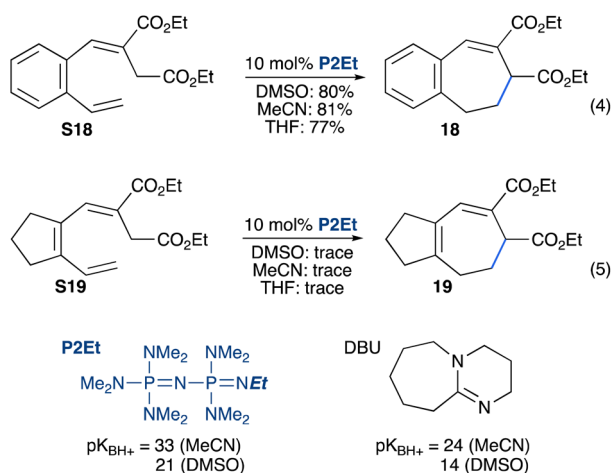
The dichotomy in the relative stabilities of the acyclic and cyclic anions suggested that a chain reaction may be possible for the aromatic system, with the anionic product of one electrocyclicization event acting as the base for the next electrocyclicization. To gain insight into this mechanistic scenario we studied the hypothetical reaction of a cycloheptadienyl anion removing the activated proton of the heptatriene substrate to give the corresponding cycloheptadiene and the heptatrienyl anion, for both the parent aromatic and aliphatic systems. In the aromatic case this elementary step is exergonic by -17.5 kcal mol⁻¹ and has an energy barrier of 12.5 kcal mol⁻¹ (eqn (2)).



In contrast, the aliphatic case is almost isoergonic (-0.9 kcal mol⁻¹) and has an energy barrier of 25.4 kcal mol⁻¹ (eqn (3)). These findings are consistent with the requirement of a catalytic base to cyclize the aromatic substrate (S3 to 3, Table 2) and the need to use a stoichiometric base to cyclize the aliphatic substrate (S1 to 1, Table 1).



To determine if a chain reaction is indeed possible, we subjected these substrates to electrocyclization conditions using a strong phosphazene base (P2Et), which has a considerably greater pK_{BH^+} than DBU in organic solvents.^{28,29} This avoids the possibility of the electrocyclization proceeding through a closed cycle (as in Fig. 2) because the product anion cannot deprotonate the phosphazenum conjugate acid. Treatment of the aromatic substrate **S18** with 10% of the P2Et phosphazene base in organic solvents (DMSO, MeCN and THF) resulted in complete conversion of the substrate (NMR) and provided isolated yields of 77–81% of product **18** (eqn (4)). In contrast, when the aliphatic substrate **S19** was subjected to the same conditions, little conversion was observed by NMR spectroscopy (eqn (5)).



The observations and calculation for the electrocyclization of aromatic substrates using a catalytic base and proceeding through a chain reaction mechanism are summarized in Fig. 5. This clearly illustrates that although the equilibrium between the acyclic and cyclic anion is slightly favoured towards the acyclic form, it is pulled forward by the exergonic protonation of the cyclic anion by an equivalent of substrate acting as the acid.

5. Discussion

Although the electrocyclization of heptatrienyl anions has been known for over half a century, it has remained obscure and underdeveloped as a tool for synthesis. This may be partly due to

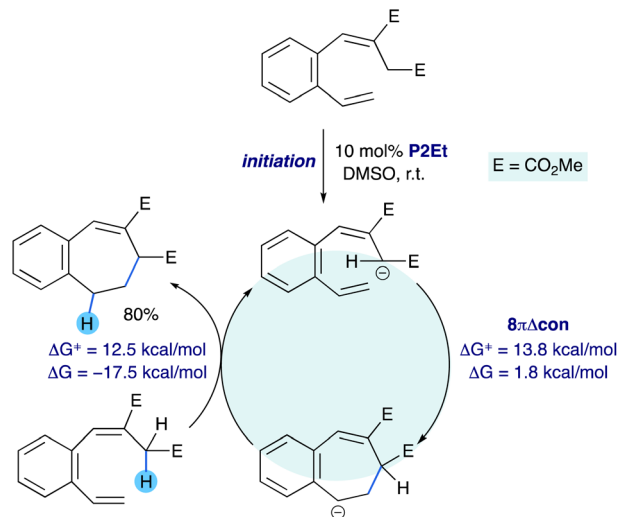


Fig. 5 Chain reaction mechanism for the electrocyclization of heptatrienyl anions bearing an aromatic backbone.

the harsh conditions originally reported for anion generation, which lowers functional group tolerance. Indeed, all known examples¹⁴ of electrocyclization of heptatrienyl anions use strongly basic intermediates. Given the relative dearth of methods for cycloheptane synthesis we set out to transform this fundamental reactivity into a broadly useful method. Our reaction design stems from the recognition that sigma bond formation is a considerable driving force for electrocyclizations, and that therefore anion basicity in the present electrocyclization manifold should be largely irrelevant as long as both acyclic and cyclic anions in the equilibrium are similarly basic. The relative acidity (or basicity of the resulting anions) can be tuned by installation of suitable electron withdrawing groups at strategic positions to stabilize the anions. The position of these groups is guided by the nature of the highest occupied molecular orbitals of the acyclic and cyclic anions, as we show in Fig. 2. In this initial report we utilized substrates with electron-withdrawing groups with a 1,2-relative disposition, however, as Fig. 2 makes clear, there are other substitution patterns (e.g. 1,4-disubstitution, and so on) that will also achieve this strategic goal. Finally, we originally envisioned a closed catalytic cycle in which a mild exogenous base would serve to generate the stabilized heptatrienyl anion and subsequently protonate the cycloheptadienyl anion.

During our studies we found that aliphatic heptatriene substrates cyclized upon treatment with stoichiometric amounts of the mild organic base DBU. These are the mildest conditions for electrocyclization of heptatrienyl anions ever reported and on their own constitute a useful addition to the synthetic toolbox. Surprisingly, the aliphatic substrates and their products are somewhat unstable, and in addition, other substrates could not be easily made by our synthetic strategy. This obstacle will likely yield other variants of this electrocyclization, using substrates with electron-withdrawing groups at different positions of the heptatrienyl system, for example. We then focused our efforts to the more stable substrate class bearing aromatic rings. These also cyclize under very mild

conditions, using DBU as the base, and to our delight the reaction also proceeds using a catalytic base. It bears emphasizing that this is the first demonstration of catalysis for the electrocyclization of heptatrienyl anions.

The divergence in reactivity between the two substrate classes led us to explore the reactions by computation. The reactions have similar activation barriers and thermodynamic driving forces but differ in the relative stability of the acyclic and cyclic anions. Mechanistic experiments using the aromatic substrates and catalytic amounts of strong phosphazene base, which forms a weak conjugate acid, support a mechanism in which the cyclized anion acts as the base for the next electrocyclization event. This is not possible in the electrocyclization of aliphatic substrates because the resulting cycloheptadienyl anion is more stable than the acyclic anion. In contrast, the cyclized anion derived from the aromatic substrate is slightly less stable than the acyclic anion and can deprotonate another molecule of substrate, resulting in a chain reaction mechanism.

6. Concluding remarks

Overall, in this study we have disclosed new design principles for the electrocyclization of heptatrienyl anions, which we hope to extend to other substrate classes in the future. Implementation of this design resulted in the mildest conditions for electrocyclization of heptatrienyl anions ever reported. Finally, we also report the first examples of catalytic electrocyclization of heptatrienyl systems and provide evidence for a chain reaction process.

Author contributions

Faizan Rasheed conducted proof-of-principle experiments, helped with substrate scope studies and helped manage the project. Andrei Nikolaev provided mechanistic insights, conducted experiments that revealed the chain reaction mechanism, and helped with substrate scope. Anmol Dhesi conducted reaction optimization with the aliphatic substrates and helped with substrate scope. Tao Zeng conducted all theoretical work. You Xuan Guo conducted optimization studies with the aromatic substrates and helped with substrate scope. Yarkali Krishna and Samira Komijani helped with substrate scope. Arturo Orellana conceived of this study and managed the project.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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