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Synchronized Aromaticity as an Enthalpic Driving Force for the Aromatic Cope Rearrangement

David J. Babinski,[†] Xiaoguang Bao,[‡] Marie El Arba,[†] Bo Chen,[‡] David A. Hrovat,[‡] Weston Thatcher Borden,*[,‡] and Doug E. Frantz*[,†]

[†]Department of Chemistry, The University of Texas at San Antonio, San Antonio, Texas 78249, United States

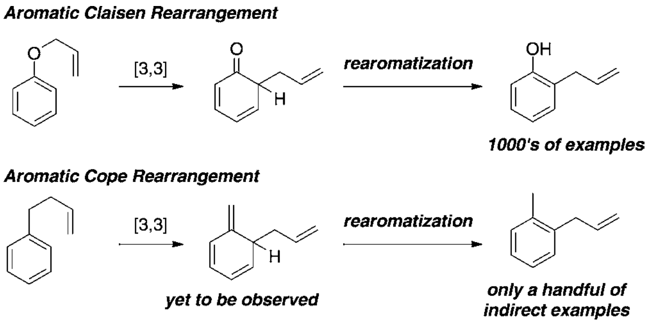
[‡]Department of Chemistry and Center for Advanced Scientific Computing and Modeling, University of North Texas, 1155 Union Circle No. 305070, Denton, Texas 76203-5017, United States

Supporting Information

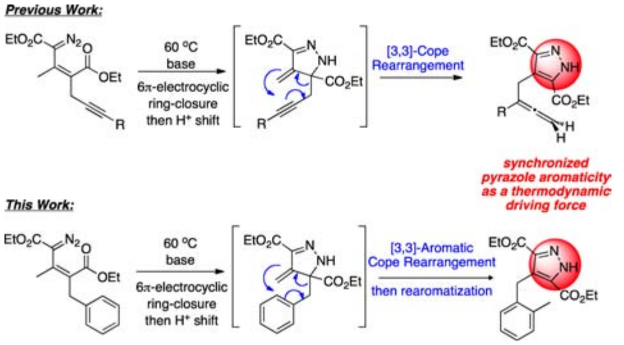
ABSTRACT: We report herein experimental and theoretical evidence for an aromatic Cope rearrangement. Along with several successful examples, our data include the first isolation and full characterization of the putative intermediate that is formed immediately after the initial [3,3] sigmatropic rearrangement. Calculations at the B3LYP/6-31G(d) level of theory predict reaction energy barriers in the range 22−23 kcal/mol for the [3,3]-rearrangement consistent with the exceptionally mild reaction conditions for these reactions. The experimental and computational results support a significant enthalpic contribution of the concomitant pyrazole ring formation that serves as both a kinetic and thermodynamic driving force for the aromatic Cope rearrangement.

Over 70 years have passed since the Cope [3,3] sigmatropic rearrangement was first discovered.[1] Initially viewed as a purely mechanistic curiosity, the past seven decades have seen the Cope rearrangement capture a broad audience of experimental and theoretical chemists who have advanced its synthetic utility and debated its chameleonic mechanistic possibilities.[2,3] However, the Cope rearrangement still suffers from a limitation that its older cousin, the Claisen rearrangement, does not. For instance, although the aromatic Claisen rearrangement is a well-known reaction that has enjoyed broad synthetic application in organic synthesis,[4] the corresponding all-carbon variant (aromatic Cope rearrangement) has proven experimentally challenging to achieve and even more difficult to confirm (Scheme 1). While anecdotal examples have appeared in the literature, with indirect evidence from formation of products attributed to a potential aromatic Cope rearrangement, to this day the direct observation of a [3,3]-rearrangement on a simple benzene ring has eluded experimental verification.[5−9]

Scheme 1. Aromatic Claisen vs Aromatic Cope Rearrangement



Scheme 2. Cope Rearrangement Driven by Synchronized Aromaticity



During our recent work on the synthesis of substituted pyrazoles, we identified an aliphatic Cope rearrangement that sparked our interest due to the surprisingly mild reaction conditions under which it occurred (Scheme 2).[10] We attribute the facility of this [3,3]-rearrangement to the concomitant generation of an aromatic pyrazole ring during product formation which provides the enthalpic driving force for this reaction. Various driving forces have been used to facilitate Cope rearrangements including relief of ring strain,[11] formation of π-bonds to heteroatoms (i.e., the oxy-Cope and aza-Cope),[12] anionic acceleration,[13] and metal[14] and enzymatic catalysis.[15] However, as far as we are aware, using synchronous generation of aromaticity to facilitate the Cope rearrangement has received little attention.[16−18] Here, we report our preliminary studies on the application of this approach to realizing an aromatic Cope rearrangement involving a simple benzene ring.

Heating vinyl diazoacetate **1** in neat *N*-methylmorpholine (NMM) gave two products in comparable yields (Scheme 3). **3** was immediately identified as the result of a [1,3]-alkyl shift, a type of product observed previously during our work on the aliphatic Cope rearrangements of pyrazoles.[10,17] The structure of **2**, however, required us to entertain the possibility of a [3,3]

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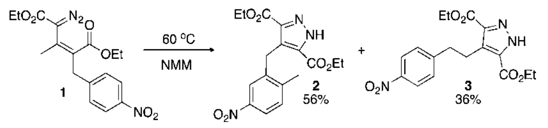
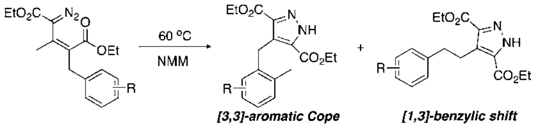
Scheme 3. Discovery of the Aromatic Cope Rearrangement of 1



sigmatropic rearrangement involving the benzene ring of **1** (an aromatic Cope rearrangement).

Before undertaking mechanistic studies on this unexpected result, we wanted to identify reaction conditions that would suppress the formation of the [1,3]-benzylic shift product **3** and favor the formation of product **2**. Competing sigmatropic rearrangements are common and in many cases unavoidable.[19] However, significant evidence points to [1,3]-benzylic shifts occurring via a radical pathway.[16,20] With this in mind, we set out to control the product outcome in the present reaction with simple adjustments to the reaction conditions (Table 1). For example, the addition of AIBN (3 equiv) swings the outcome completely in favor of the [1,3]-alkyl shift product in 64% assayed yield (Table 1, entry 2). Yet, performing the reaction in the presence of 3 equiv of BHT (butylated hydroxytoluene) provides exclusive formation of the aromatic Cope product **2** in 86% assayed yield (Table 1, entry 3).[21]

Table 1. Preliminary Scope of the Aromatic Cope Rearrangement



entry[a]	R	additive	[3,3]	[1,3]
1	4-NO_2	none	56%[c]	36%[c]
2		AIBN[b]	<1%[c]	64%[c]
3		BHT[b]	86%[c]	<1%[c]
		BHT[b]	68%[d]	
4	2-NO_2	BHT[b]	69%[d]	
5	4-CF_3	BHT[b]	42%[d]	<1%
6	4-Cl	BHT[b]	30%[d]	<1%
7	3-NO_2	BHT[b]	28%[d,e]	24%[d]
8	H	BHT[b]	13%[d,f]	<1%[d]
9	4-OMe	BHT[b]	<1%[f,g]	<1%

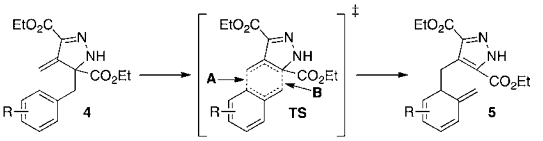
[a]Reactions performed at 0.2 M in neat NMM. [b]3.0 equiv. [c]HPLC assay yields using an analytical standard of each product. [d]Isolated yield. [e]Only the 1,2,4-substituted regioisomer is formed (see SI for details). [f]Reaction performed at reflux. [g]Complex mixture with no detectable [3,3]- or [1,3]-products by LC/MS (see SI).

Extension of these latter reaction conditions to a series of additional substrates reveals that the aromatic Cope products not only are obtainable but also, in many cases, can be isolated in reasonable yields when electron-withdrawing groups are present in the 2- and 4-positions. Important to note, however, is the low yield of the aromatic Cope product with a 3-NO_2 substituent and an unsubstituted benzene ring (Table 1, entries 7 and 8, respectively) and the failure of the reaction with a 4-OMe substituent (Table 1, entry 9).

The results summarized in Table 1 begin to shed light on why an aromatic Cope rearrangement is feasible with these substrates. We believe that the resonance energy associated with the synchronized development of aromaticity in the pyrazole ring[22] provides enough compensation to balance the energetic penalty for disrupting benzene aromaticity in the transition state. However, even if the [3,3]-rearrangement becomes thermodynamically accessible, the barrier to rearomatization by proton or H-atom transfer may, as suggested by Doering,[7] ultimately determine the success or failure of an aromatic Cope rearrangement. Thus, if the rearomatization step proceeds through a deprotonation/reprotonation pathway and is in fact rate-limiting, the relative success of reactions in which the reactant has electron-withdrawing groups in the 2- or 4-positions becomes explicable (entries 3–6, Table 1). Likewise, the poor yield with 3-NO_2 and with an unsubstituted benzene ring, along with the complete failure of the reaction with 4-OMe, are all consistent with a rate-limiting base-mediated proton transfer. Finally, the ability to preferentially direct the reaction to the aromatic Cope product with BHT or to the [1,3]-benzylic shift product with AIBN suggests that a common reaction intermediate can be kinetically partitioned between an ionic or radical pathway (see below).

To explore the energetics of the aromatic Cope rearrangement, we performed B3LYP calculations,[23] using the 6-31G(d) basis set.[26] B3LYP/6-31G(d) calculations have been previously found to provide very accurate energetics for the Cope rearrangements of phenyl-substituted 1,5-hexadienes and for the aromatic Claisen rearrangement.[27] Our calculations on aromatic Cope rearrangements were carried out with the Gaussian 09 suite of programs.[28] The first set of calculations set out to determine the enthalpies of the transition state and resulting semi-benzene intermediate in the [3,3] sigmatropic rearrangement for each experimental example presented in Table 1. The computational results are summarized in Table 2.[29]

Table 2. B3LYP/6-31G(d) Enthalpies (kcal/mol) and Lengths of Bonds Formed (A) and Broken (B) in the Transition Structure for the [3,3]-Aromatic Cope Rearrangement of 4 to 5

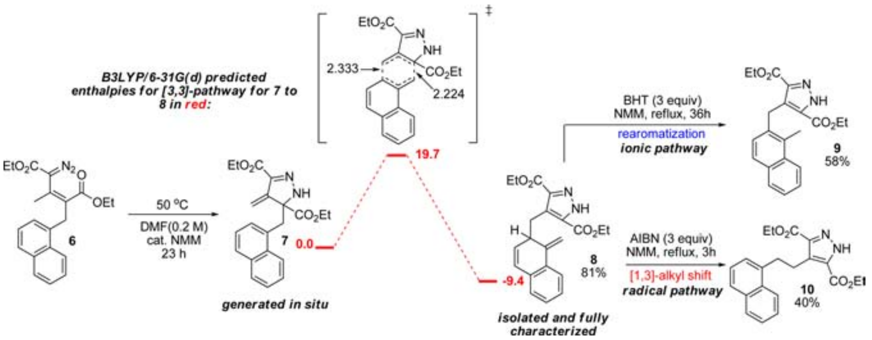


reactant	R	$\Delta H^{\ddagger a}$	ΔH^{a}	A[b]	B[b]
4a	4-NO_2	22.0	−0.4	2.355	2.369
4b	2-NO_2	21.1	−1.4	2.362	2.373
4c	4-CF_3	22.5	−0.9	2.300	2.309
4d	4-Cl	23.2	0.2	2.301	2.329
4e[c]	3-NO_2	23.0	−0.4	2.213	2.221
4f	H	23.6	1.1	2.292	2.328
4g	4-OMe	22.6	0.0	2.321	2.421

[a]Energies in kcal/mol. [b]Bond lengths in Å. [c]Calculations performed on same regioisomer produced experimentally (Table 1).

Several conclusions can be drawn from the results of these calculations. First, the driving force for the enthalpic contribution of synchronous formation of aromaticity in the pyrazole ring during the [3,3]-rearrangement from **4** to **5** is reflected in both $\Delta H^{\ddagger}$ and ΔH. The calculated transition state energies in Table 2 for a concerted [3,3] sigmatropic rearrangement from **4** to **5** are ∼10 kcal/mol lower than for the prototypical aliphatic Cope and aromatic Claisen rearrangements (∼30–35 kcal/mol).[30] Our calculations also find that the ester group, attached to the saturated carbon in **4**, which becomes conjugated with the

Scheme 4. Experimental and Theoretical Data for Semi-naphthalene Intermediate 8 and Subsequent Ionic and Radical Pathways



pyrazole ring in **5**, is responsible for lowering $\Delta H^{\ddagger}$ by ~7 kcal/mol and ΔH by ~8 kcal/mol (see Supporting Information (SI)). Also, the calculated barrier heights in Table 2 are consistent with the comparatively low temperature at which these rearrangements proceed. More importantly, the calculated enthalpy differences between the reactant **4** and the semi-benzene intermediate **5** are very small. In each case the computed ΔH predicts that, at equilibrium, significant amounts of **5** would be available for rearomatization via an irreversible base-mediated proton transfer to the aromatic Cope product. What is not explained by the enthalpies in Table 2 are the low yields obtained when R = 3-NO_2, H, and 4-OCH_3. Yet, as discussed above, we believe rearomatization of **5** by de-/reprotonation is less favorable in these cases where nonproductive pathways from this semi-benzene intermediate can effectively compete with the rearomatization step.

Given the predictions from our theoretical studies that the initial [3,3] sigmatropic rearrangement is nearly thermoneutral and our experimental evidence suggesting the rearomatization step may in fact be rate-limiting, we surmised that the isolation of **5** should be feasible. We hypothesize that replacing the benzene ring in **4** with a naphthalene ring might render the initial [3,3]-rearrangement appreciably exothermic thus making possible the isolation of the intermediate formed in this step. Indeed, when vinyl diazoacetate **6** was treated with catalytic amounts of NMM in DMF at 50 °C, the corresponding semi-naphthalene intermediate **8** was isolated in 81% yield (Scheme 4).

The remarkable success of this reaction is explained by the B3LYP/6-31G(d) finding that formation of **8** from **7** has a predicted $\Delta H = -9.4$ kcal/mol. It is important to note that the isolation and characterization of **8** represents the first direct evidence for a [3,3]-aromatic Cope rearrangement.

The isolation of **8** also provided us with the opportunity to confirm the existence of two partitioning pathways, one leading to the rearomatized product of an aromatic Cope rearrangement and the other to the [1,3]-alkyl shift product. As expected, heating of **8** in NMM with 3 equiv of BHT at reflux for 36 h provided the aromatic Cope product (**9**) cleanly in 58% isolated yield (Scheme 4). Conversely, treatment of **8** with AIBN (3 equiv) in refluxing NMM diverts the pathway to the [1,3]-alkyl shift product (**10**) in 40% yield after 3 h. This latter result provides permissive evidence that the source of [1,3]-alkyl shift products in these reactions is a free-radical catalyzed reorganization of the semi-benzene intermediate.[31]

This hypothesis also explains the ability to control the final product formed in the aromatic Cope rearrangement by simple addition of a radical initiator (AIBN) or inhibitor (BHT). More broadly, our results suggest the realistic opportunity to divert the semi-benzene intermediate in these reactions, formed during the course of an aromatic Cope rearrangement, from rearomatization to alternative synthetically useful pathways.

In conclusion, the success of the aromatic Claisen rearrangement has been attributed to a combination of thermodynamic driving force (strong C═O bond) and rapid regeneration of aromaticity via tautomerization. Past attempts at carrying out successful aromatic Cope rearrangements have failed because one or both of these requirements were not satisfied.

Here, we report that synchronous formation of pyrazole aromaticity in the [3,3] sigmatropic rearrangement of **4** provides not only a strong thermodynamic driving force for the rearrangement to **5** but also a low enthalpy barrier. The reaction conditions allow rearomatization of the putative semi-benzene intermediate presumably via a base-promoted de-/reprotonation step that is facilitated by electron-withdrawing groups in the 2- and 4-positions of the benzene ring.

Studies are currently underway to develop a more thorough mechanistic understanding of these reactions and to expand the concept of using synchronized aromaticity to facilitate other sigmatropic rearrangements.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures, full characterization of all new compounds, ^1H and ^{13}C NMR spectra, the optimized B3LYP/6-31(d) geometries and energies of all the molecules on which calculations were performed, and complete ref 28. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

doug.frantz@utsa.edu

Notes

The authors declare no competing financial interest.

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