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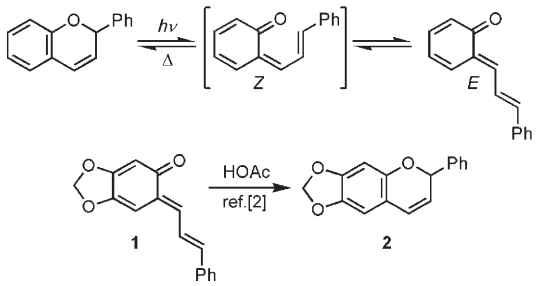
# Mechanistic Investigations of the Acid-Catalyzed Cyclization of a Vinyl *ortho*-Quinone Methide

**Lee M. Bishop,[a] Michael Winkler,*[b] Kendall N. Houk,[c] Robert G. Bergman,*[a] and Dirk Trauner*[a]**

The reversible ring opening of chromenes to yield vinyl *ortho*-quinone methides (vinyl *o*-QMs) has been the subject of extensive studies. This reaction is one of the first photochromic processes to be investigated and has important applications in certain materials, for example, in photochromic ophthalmic lenses.[1] Whereas the photochemical ring opening is well understood, the thermal reverse reaction has received relatively little attention. This is mostly due to difficulties with isolating stable vinyl *o*-QMs. These typically contain *E*-configured *exo*-alkylidene bonds preventing them from undergoing oxa-6π electrocyclizations (Scheme 1).[2–4] The kinetics of vinyl *o*-QM cyclization or the possibility of catalyzing this processes have not been investigated in detail.

In the context of our ongoing studies on the catalysis of electrocyclizations, we became interested in a report by Jurd describing an acid-promoted cyclization of the isolable vinyl *o*-QM **1** to chromene **2** (Scheme 1).[2] We now present a detailed study of this reaction, which has general implications for the thermal cyclization of vinyl *o*-QMs to afford chromenes.




Scheme 1. Cyclization of vinyl *ortho*-quinone methides.

Vinyl *o*-QM **1** was prepared through oxidation of phenol **3** according to literature procedures (Scheme 2).[2] The *E* configuration of the *exo*-alkylidene bond was unequivocally established by detailed NMR studies and X-ray crystallography (see Supporting Information). Interestingly, attempts to prepare a second vinyl *o*-QM from phenol **4** under similar conditions resulted in the isolation of compound **5**, the result of a Diels–Alder dimerization of two vinyl *o*-QM molecules.[3] The structure of this unusual dimer was confirmed by X-ray crystallography (Figure 1). Whereas *o*-QM dimerization is well established in the literature,[5] this appears to

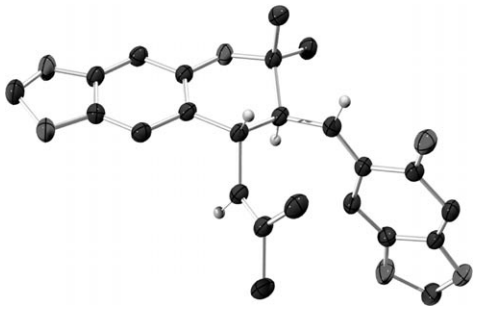


Figure 1. ORTEP diagram of **5** at the 50% probability level. Some hydrogen atoms have been removed for clarity.

[a] L. M. Bishop, Prof. Dr. R. G. Bergman, Prof. Dr. D. Trauner
Department of Chemistry
University of California, Berkeley
Berkeley, CA 94720-1460 (USA)
Fax: (+1) 510-642-7714
E-mail: rbergman@berkeley.edu
trauner@berkeley.edu

[b] Dr. M. Winkler
Institut für Organische Chemie
Universität Würzburg
Am Hubland
97074 Würzburg
Fax: (+49) 931-888-4606
E-mail: Michael.Winkler@uni-wuerzburg.de

[c] Prof. Dr. K. N. Houk
Department of Chemistry and Biochemistry
University of California, Los Angeles
Los Angeles, CA 90095-1569 (USA)
Fax: (+1) 310-206-1843

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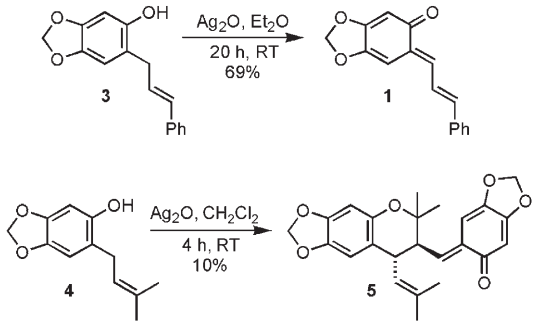
be the first example that leaves an *o*-QM moiety intact. The analogous dimerization was not observed with compound **1** under various conditions.

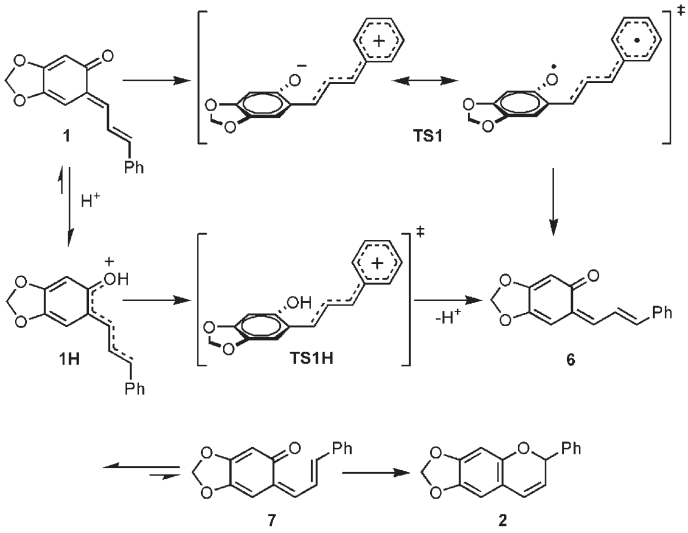



Scheme 2. Preparation of *ortho*-quinone methides.

With vinyl *o*-QM **1** in hand, we proceeded to study its reactivity. Kinetic investigation of the uncatalyzed cyclization of **1** to **2** revealed the sensitivity of the rate of this reaction to light, oxygen, and adventitious acid. However, reproducible kinetic data could be obtained in the absence of light, under air-free conditions and in the presence of Proton-sponge. Monitoring the cyclization by $^1$H NMR spectroscopy revealed quantitative formation of **2** with no observable intermediates. Kinetic data fit a first order exponential decay process, with an $k_{obs}$ of $4.2(1)\times10^{-5}$ s$^{-1}$ at 50 °C.

Given the *E* configuration of the *exo*-alkylidene bond of **1**, we hypothesized that the rate-limiting step in the cyclization of **1** to **2** was the double-bond isomerization and not the subsequent electrocyclization. The activation parameters for the thermal reaction support this hypothesis (Table 1). A relatively modest enthalpy of activation was measured for this process, which we attribute to the aromatization of the quinoidal system in the *exo*-alkylidene bond isomerization transition state (Scheme 3, **TS1**). The reaction also exhibits a highly negative entropy of activation, revealing a high degree of order in the transition state of the rate-limiting step, relative to the vinyl *o*-QM reactant. Entropies of activation for oxa-6π electrocyclizations are typically around −12 e.u.,[6] which is much less negative than the value measured for this vinyl *o*-QM cyclization. However, entropies of activation for the isomerization of push-pull alkenes are quite negative, an effect that has been attributed to solvent reorganization on going from the relatively non-polar reactant to the highly polar transition state.[7] This could also be the case for the cyclization of **1**, as DFT calculations suggest the *E*/*Z* isomerization transition state is highly polar.[8] Thus, these activation parameters are consistent with a stepwise process, wherein a rate-limiting double bond isomerization step is followed by a faster oxa-6π electrocyclization.

Next, we proceeded to investigate the influence of Brønsted acids on the rate of the cyclization. Catalytic amounts of chloroacetic acid (0.23 equiv) led to a 200-fold rate acceleration at 21 °C ($k_{obs}=1.31(2)\times10^{-3}$ s$^{-1}$).[9] Interestingly, a new species was observed by $^1$H NMR spectroscopy upon addition of chloroacetic acid to **1**, which suggested the vinyl *o*-QM was being appreciably protonated with substoichiometric amounts of acid. Low temperature NMR titration (Figure 2) revealed near quantitative protonation of **1** using nine equivalents of chloroacetic acid. Interestingly, this effect was not observed using acetic acid, which allows us to estimate the p$K_a$ of the protonated vinyl *o*-QM **1H** to be approximately 4. Furthermore, the unusually high p$K_a$ of **1H** allowed us to observe substrate-saturation kinetics using chloroacetic acid as catalyst.[10]




Scheme 3. Proposed pathways for the thermal and acid-catalyzed reactions.

Table 1. Activation parameters measured in $CD_2Cl_2$ for the thermal and catalyzed (9 equiv acid) cyclization of **1** to **2**.

| | Thermal | Catalyzed |
|---|---|---|
| $\Delta H^{\neq}$ [kcal mol$^{-1}$] | 13.3(4) | 20.1(4) |
| $\Delta S^{\neq}$ [e.u.] | −38(5) | −4.1(1) |
| $\Delta G^{\neq}_{298}$ [kcal mol$^{-1}$] | 24.6(8) | 21.3(4) |

In order to determine the activation parameters for the rate-limiting step in the catalyzed reaction, kinetic data were obtained under acid saturation to assure that we were monitoring only cyclization of **1H** with no effect from the **1**-**1H** pre-equilibrium. Both the enthalpy and entropy of activation for the catalyzed reaction increase dramatically as compared to those of the thermal reaction (Table 1). The less negative entropy of activation for the catalyzed reaction suggests only a small change in polarity between the protonated *o*-QM reactant and the isomerization transition state. This observation is consistent with the small polarity change that would be expected under acid-saturated conditions on going from the cationic *o*-QM **1H** to the cationic isomerization transition state **TS1H** (Scheme 3). The increased enthalpy of activation must be understood in terms of the basicity of **1**. Protonation of **1** results in aromatization of the quinoidal system giving a doubly benzylic cation. This aromatization enthalpically stabilizes the vinyl *o*-QM reactant

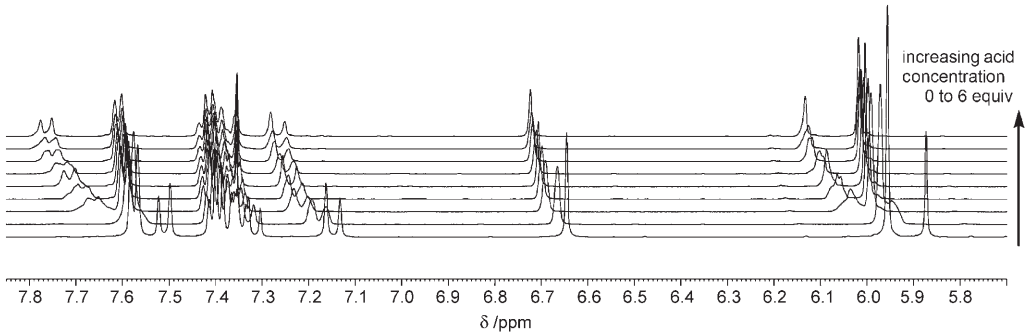



Figure 2. NMR titration of **1** with $ClCH_2COOH$ at −40 °C.

relative to the isomerization transition state. This is in contrast to the thermal reaction, where aromatization of the quinoidal system occurs only once the transition state is reached, resulting in a lower enthalpy of activation for the thermal process.[11]

In parallel to our experimental work, the energetics of the thermal and catalyzed reactions were modeled by density functional theory calculations. The pathway whereby *E*/*Z* isomerization precedes s-*cis*/s-*trans* isomerization was modeled along with the pathway whereby *E*/*Z* isomerization is preceded by s-*cis*/s-*trans* isomerization at the UB3LYP/6-31G* level (Figure 3). According to these calculations, the *exo*-alkylidene bond isomerization is the rate-limiting step in the thermal cyclization, having a Gibbs free energy barrier of 29.3 kcal mol$^{-1}$, which is over 10 kcal mol$^{-1}$ higher than the electrocyclization barrier. The lowest energy pathway for the thermal reaction occurs through *exo*-alkylidene bond isomerization of **1** to give the *Z o*-QM **6**, which can then undergo s-*cis*/s-*trans* isomerization ($\Delta G^{\neq} = 13.8$ kcal mol$^{-1}$) to give **7**, which is poised to undergo an oxa-6π electrocyclization ($\Delta G^{\neq} = 19.8$ kcal mol$^{-1}$) to give chromene **2**. Thus, these calculations mirror our experimental evidence that the isomerization, not the electrocyclization, is the rate-limiting step of the thermal cyclization.

The catalyzed reaction was modeled by protonation of the carbonyl oxygen of **1** *anti* to the *exo*-alkylidene bond. The calculated lowering of the catalyzed *exo*-alkylidene *E*/*Z* isomerization barrier by 4–5 kcal mol$^{-1}$,[12] relative to the thermal reaction barrier, is in reasonable agreement with the experimental observation of a 3.3 kcal mol$^{-1}$ lowering in the Gibbs free energy of activation. The measured activation parameters indicate that acid-catalysis is due to a strong increase in the entropy of activation that more than outweighs the increased enthalpy of activation. The gas-phase computations, on the other hand, that do not include solvent effects, indicate that the catalyzed reaction is enthalpically more favorable than the thermal isomerization with very minor contributions from entropy. Inasmuch as the DFT calculated energies of **TS1** and **TS1H** are accurate, the comparison of calculated and measured activation parameters thus gives another clue to the decisive role of solvent effects in the *E*/*Z* isomerization barrier of push–pull substituted alkenes.[7] The computations also show that upon protonation of **1**, the s-*cis*/s-*trans* isomerization and electrocyclization energy barriers increase, relative to the unprotonated reaction (**TS2H/TS3H** vs **TS2/TS3** and **TS5H** vs **TS5**, respectively). The former remain slightly below the *E*/*Z* isomerization barrier, whereas the latter increases drastically. We propose that the catalyzed reaction proceeds first by rate-limiting isomerization of **1H** to yield protonated *Z o*-QM **6H**. Because the s-*cis*/s-*trans* isomerization and electro-

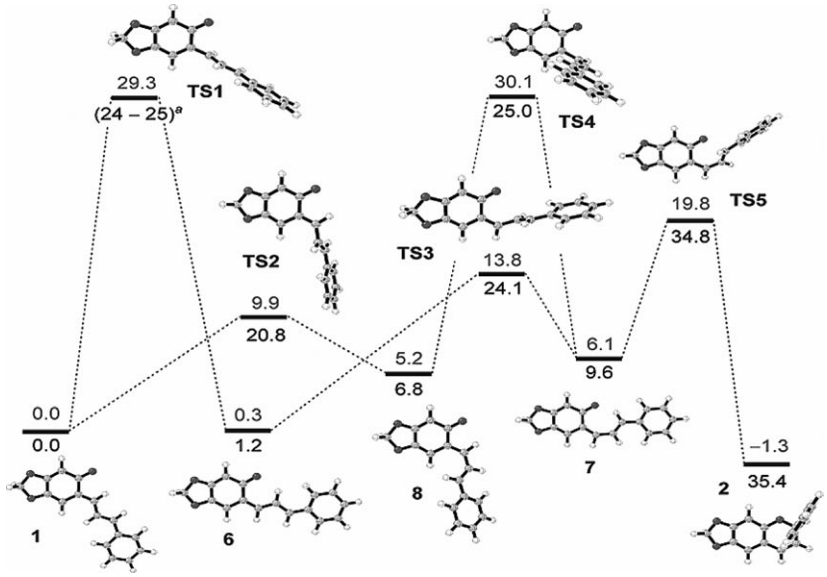



Figure 3. Relative Gibbs free energies [kcal mol$^{-1}$] of the thermal (above) and carbonyl-protonated (below) pathways (conversion of 1 to 2) computed at the UB3LYP/6-31G* level of theory. Structures shown refer to the thermal reaction. [a] Consult ref. [12].

cyclization energy barriers increase for **6H** relative to **6**, we believe that the transformation from **6H** to product then occurs on the thermal reaction pathway via **6** to **7** to **2** (Scheme 3).

Interestingly, calculations indicate that the chromene product is unstable towards protonation. The protonated chromene **2H** occupies a very flat minimum on the potential energy surface and after inclusion of zero-point vibrational energy corrections, the corresponding ring-opening transition state **TS5H** disappears as a stationary point, so that ring-opening of the protonated chromene becomes barrierless. Once formed, however, the chromene product is presumably not basic enough to be protonated and is therefore stable under the conditions used in our experiments.

In summary, we have provided evidence that the cyclization of *E*-configured vinyl *o*-QMs involves a relatively slow acid-catalyzed *exo*-alkylidene bond isomerization followed by faster oxa-6π electrocyclization. Computations indicate that the overall reaction is catalyzed by Brønsted acids, but the oxa-6π electrocyclization step itself is not prone to such catalysis. The vinyl *o*-QM was found to be surprisingly basic, allowing for quantitative protonation with relatively weak acids. In addition, we have identified a new mode of Diels–Alder dimerization of vinyl *o*-QMs. The factors determining the stability of *o*-QMs towards dimerization are currently under investigation in our laboratories.

## Experimental Section

Experimental procedures, characterization data for products, and complete citation of reference [8] are available in the Supporting Information.

## Acknowledgements

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**Keywords:** activation parameters · alkenes · density functional calculations · dimerization · isomerization

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[8] The calculated dipole moments of **TS1** and **1** are 4.56 and 4.52 D, respectively. The intrinsic molecular charge distribution, as conjectured from natural population analysis, is also comparable for both stationary points. The strongly negative entropy of activation for the *E*/*Z* isomerization step might be attributable to the fact that the transition state is polar in all three spatial directions, whereas **1** is a planar species, resulting in stronger solvation of the former. All calculations have been carried out at the B3LYP/6-31G* level using Gaussian 03: M. J. Frisch, et al. Gaussian 03; Gaussian, Inc.: Pittsburgh PA, **2003**. See the Supporting Information for complete citation. All RDFT stationary points have been checked for triplet instabilities by calculating the eigenvalues of the Hermitian stability matrices. UDFT energies are reported throughout whenever an external instability was found.
[9] Kinetic data were not obtained for the thermal reaction at 21 °C. This rate acceleration is based on extrapolation of the thermal Eyring plot.
[10] A kinetic isotope effect of 1 using $ClCH_2COOD$ was measured under acid-saturation; see Supporting Information.
[11] From the available data it cannot be determined conclusively that the enthalpy-entropy compensation effect observed is not simply a result of the fact that the enthalpy and entropy are both derived from the same data set and are thus not statistically independent. See also: W. Linert, R. F. Jameson, *Chem. Soc. Rev.* **1989**, *18*, 477–505.
[12] Despite several attempts, **TS1H** could not be located as a stationary point on the PES at the RB3LYP or UB3LYP level. Given the almost identical energies of **TS1** and **TS4**, and according to single point energy calculations, the energy of **TS1H** relative to **1H** is estimated to be 24–25 kcal mol$^{-1}$.

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