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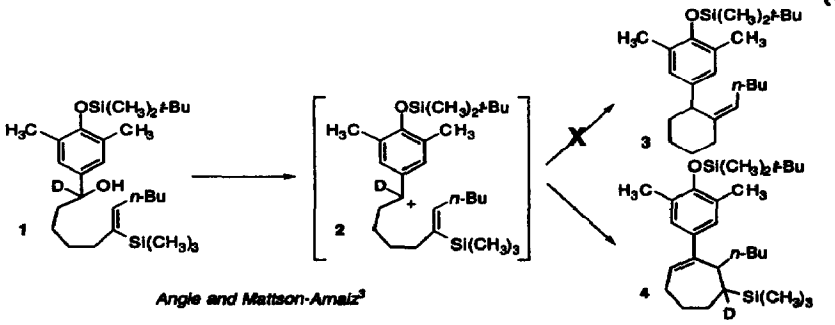
MECHANISM OF *p*-QUINONE METHIDE INITIATED CYCLIZATION REACTIONS TERMINATED BY ALKENES: 1,2- vs. 1,3-HYDROGEN MIGRATION.

Steven R. Angle* and M. Azad Hossain
Department of Chemistry, University of California-Riverside
Riverside, California 92521-0403

Abstract: Intramolecular cyclization of benzylic cations derived from *p*-quinone methides **5** and **6**, afforded the corresponding six- or seven-membered ring products **7** or **9** depending on the substitution of the alkene. Deuterium labeling experiments indicated that formation of **9** occurred via a 1,3-hydrogen shift, whereas formation of **7** proceeded via two sequential 1,2-hydride transfers.

The use of benzylic cations to initiate cyclization reactions is well documented;[1] however, there are only a limited number of examples where simple, unactivated alkenes have been used as cyclization terminators in these reactions.[2] Previous work from our laboratory has shown that treatment of benzylic alcohol **1** affords cycloheptene **4** rather than the expected alkylidine cyclohexane **3** (equation 1).[3] Deuterium labeling studies showed that this transformation occurred via a 1,3-hydrogen migration. To our knowledge, this was the first example of a 1,3-hydrogen migration in a cycloheptyl cation.[4] The role played by the trimethylsilyl substituent in this transformation was unclear.

(equation 1)

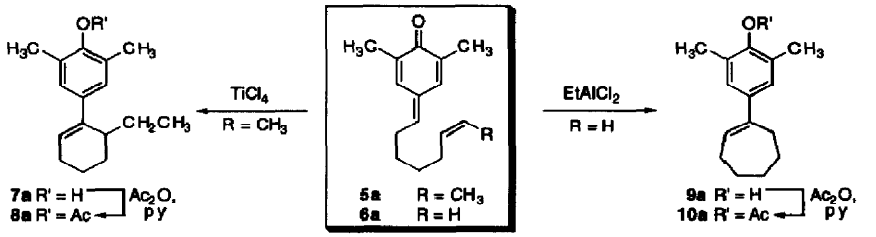


Angle and Mattson-Amaiz[3]

In other research, we found that the cyclization of quinone methide **5a** afforded unstable styrene **7a** (Scheme 1).[2] Treatment of **7a** with acetic anhydride in pyridine afforded **8a** for characterization. The similarity of the structure of **7a** to **4** raised the possibility that a similar mechanism was involved in both reactions. In an effort to investigate the generality of this type of hydrogen migration, and to determine the role played by silicon in **1**, and the methyl substituent in **5a**, we report here the benzylic cation initiated cyclization of a monosubstituted alkene **6a** and the cyclization of deuterated analogs **5b** and **6b**. Quinone methide **6a** was expected to cyclize to a cycloheptene via a secondary carbocation since the cyclization to a six-membered ring would require formation of a primary carbocation intermediate.[5]

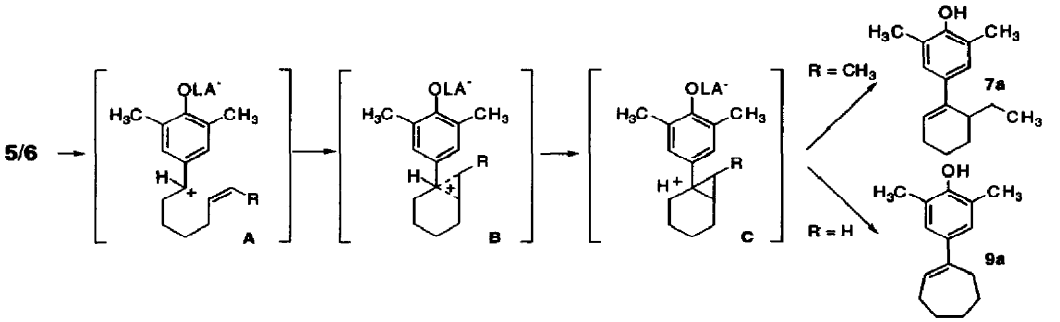
Treatment of quinone methide **6a**[6] (R = H) with $EtAlCl_2$ (10 equiv, CH_2Cl_2, 0.05 M, -78 °C, 30 min) followed by workup and acetylation (Ac_2O, py) afforded cycloheptene **10a** in 58% yield after flash chromatography (Scheme 1).[7] The isolated yield was considerably lower if the unprotected, reactive, styrene-phenol **9a** was purified, stored, or handled for any length of time. The similarity of this cyclization to the cyclization of **1** and **5a** is clearly evident, but it remained to be shown if the mechanisms of the three reactions all involve a 1,3-hydrogen shift.

Scheme 1. Cyclization of Quinone Methides 5a and 6a.



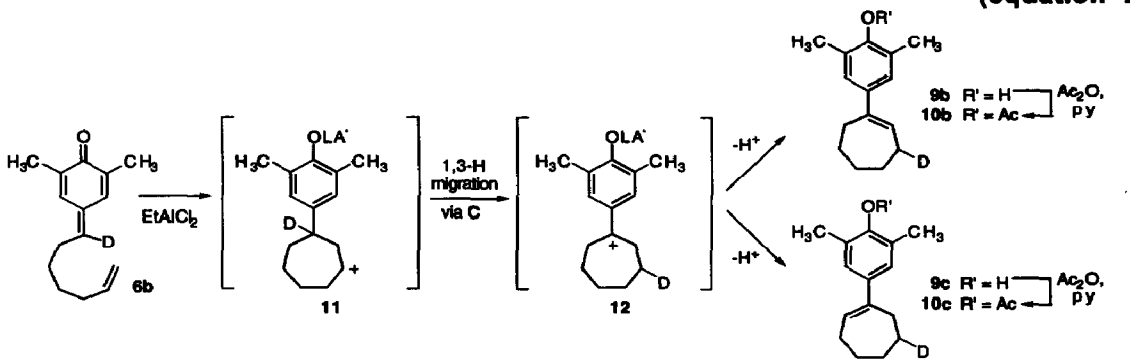
It seemed possible that the cyclization of **5a** and **6a** both involve a common mechanistic pathway. Namely, activation of the quinone methide with a Lewis acid to afford a benzylic cation (**A**) that is captured by the alkene to afford **B**, posessing a three-center two-electron bond. Then, depending upon the substitution pattern, **B** undergoes a formal 1,3-hydrogen migration to afford **7a** and **9a** via a common corner-protonated cyclopropane transition state/intermediate, **C** (Scheme 2).

Scheme 2. A Possible Common Mechanistic Pathway for the Cyclizations.



In an effort to examine the mechanisms of the reactions, deuterium labeled substrates **5b** and **6b** were prepared. Quinone methide **6b** was prepared from the corresponding phenol (> 94% d_2 by MS) by oxidation with Ag_2O (10 equiv, $CDCl_3$).[6] Cyclization of **6b** as above followed by acetylation afforded a mixture of two products **10b** and **10c** in 56% yield (1:1 ratio by ^1H NMR).[8] Deuterium analysis by mass spectrometry showed **10b/c** to be >89% d_1. This is exactly the result expected if the mechanism is as proposed in Scheme 2. Activation of **6b** by the Lewis acid followed by cyclization would afford secondary cation **11**, which may better be described as cation **B**. Migration of deuterium via transition state/intermediate **C** would then afford benzylic cation **12**. The symmetry in cation **12** is perturbed only by the deuterium atom and elimination should occur both toward and away from this substituent to afford a 1:1 mixture of **10b/c** (equation 2). This labeling study rules out alternative mechanisms such as a series of 1,2-hydrogen migrations.

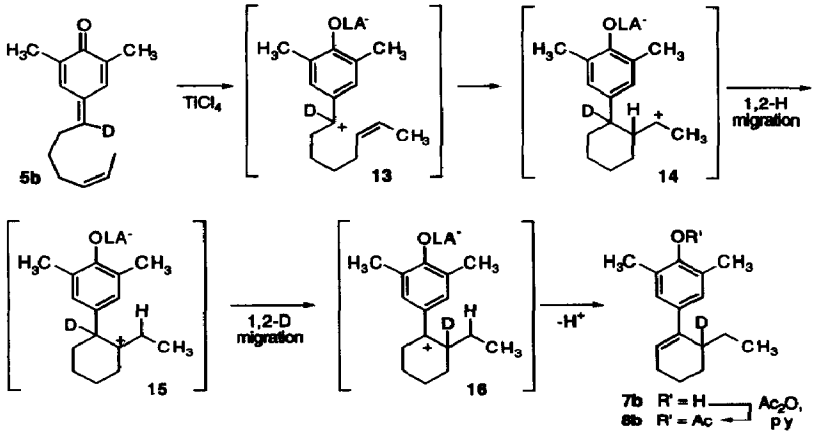
(equation 2)



Disubstituted alkene **5b** was prepared from the corresponding deuterated phenol (> 98% d_2). Lewis acid mediated cyclization afforded cyclohexene **8b** (98% d_1) in 61% isolated yield after acetylation (equation 3).[9] The position of the label was determined by ^{1}H NMR analysis and clearly shows the mechanism to involve two sequential 1,2-hydrogen migrations.[10] In this case, the initially formed benzylic cation **13** reacts with the alkene to afford secondary cation **14**, which then undergoes a 1,2-hydrogen migration to tertiary cation **15**. A second 1,2-hydrogen migration (**15** to **16**) moves the deuterium to the homobenzylic position and results in the formation of benzylic cation **16**. The regiospecific loss of the secondary hydrogen in **16** to afford alkene **7b** is likely due to the steric interaction of the ethyl and the aryl groups in the alternative tetrasubstituted alkene which would preclude any overlap of the alkene and aryl π-systems. Alkene **7b** can adopt a conformation that allows conjugation of the aryl group and the alkene.[11]

Secondary cation **14** does not undergo a 1,3-hydrogen migration. This may be due to the availability of an alternative, energetically favorable, 1,2-hydrogen migration that affords a tertiary cation (**15**). In the case of secondary cation **11** (equation 2), a similar 1,2-hydrogen migration would give another secondary cation whereas the observed 1,3-hydrogen migration gives a more stable benzylic cation.

(equation 3)



The deuterium labeling studies are consistent with reaction mechanisms involving cyclizations onto the activated quinone methides to afford cations which undergo either 1,2- or 1,3-hydrogen migrations depending on their structure and substitution. The cyclization of **5** to **9** shows that a 1,3-hydrogen migration in a cycloheptyl cation is a general process that does not require the presence of a silyl group. The generality of this type of shift in other ring systems is currently under investigation.

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6. Quinone methides **5** and **6** were prepared from the corresponding phenols by oxidation with Ag_2O: Dyall, L. K.; Winstein, S. *J. Am. Chem. Soc.* **1972**, *94*, 2196-2199.
7. Compound **10a**: clear oil; ^{1}H NMR (500 MHz, C_6D_6) δ 7.03 (s, 2 H, ArH), 6.10 (t, J = 6.7 Hz, 1 H, CH=C), 2.52 (m, 2 H, CCH_2), 2.17 (dd, J = 6.6, 11.2 Hz, 2 H, CH_2CH), 2.08 (s, 6 H, $ArCH_3$), 1.84 (s, 3 H, $C(O)CH_3$), 1.71 (m, 2 H, CH_2CH_2CH), 1.56 (m, 2 H, CH_2CH_2C), 1.49 (m, 2 H, $CH_2CH_2CH_2CH$); MS (EI, 50 eV) *m/z* 258 (M^+, 28), 216 (100), 201 (43); HRMS calcd for $C_{17}H_{22}O_2$ 258.1620, found 258.1615.
8. The position of deuterium in **10b/10c** was assigned with the aid of 2D-^{1}H NMR spectra of **10a** and the **10b/10c** mixture. Compounds **10b/10c** (1:1 mixture, ^{1}H NMR): clear oil; ^{1}H NMR (500 MHz, C_6D_6) δ 7.03 (s, 4 H, ArH), 6.10 (distorted t, J = 6.7 Hz, 2 H, CH=C), 2.53 (dd, J = 6.5, 11.1 Hz, 4 H, CCH_2), 2.17 (m, 3 H, CH_2CH and $CHDCH$), 2.08 (s, 12 H, $ArCH_3$), 1.84 (s, 6 H, $C(O)CH_3$), 1.71 (m, 4 H, CH_2CH_2CH and CH_2CHDCH), 1.56 (m, 3 H, CH_2CH_2C and $CDHCH_2C$), 1.49 (m, 4 H, $CH_2CH_2CH(H/D)CH$); MS (EI, 50 eV) *m/z* 259 (M^+, 20), 217 (100), 202 (38); HRMS calcd for $C_{17}H_{21}DO_2$ 259.1682, found 259.1680; deuterium analysis 89.0% d_1.
9. Compound **8a** has been prepared before.[2] The position of deuterium in **8b** was assigned by analysis of the ^{1}H NMR spectra for **8a** and **8b**. In particular for **8a** the signal for the allylic methine hydrogen appears at δ 2.52 (br mult) and the signal for the adjacent diastereotopic methylene hydrogens appear at δ 1.40 (mult) and δ 1.20 (mult). Deuterated analog **8b** does not show any signal at δ 2.52 and the multiplicities of the signals for the diastereotopic hydrogens of the adjacent methylene group at δ 1.40 and 1.20 are changed significantly from **8a**. Compound **8b**: clear oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (s, 2 H, ArH), 5.82 (t, J = 3.9 Hz, 1 H, CH=C), 2.33 (s, 3 H, $C(O)CH_3$), 2.20-2.12 (m, 2 H, CH_2CH), 2.13 (s, 6 H, $ArCH_3$), 1.71(apparent t, J = 5.8 Hz, , 2 H), 1.67-1.55 (m, 2 H), 1.44-1.38 (m, 1 H), 1.21-1.14 (m, 1 H), 0.82 (t, J = 7.5 Hz, 3 H, CH_2CH_3); MS (EI, 50 eV) *m/z* 273 (M^+, 18), 231 (100); HRMS calcd for $C_{18}H_{23}DO_2$ 273.1839, found 273.1826; deuterium analysis 98.0% d_1.
10. For a leading reference to 1,2-hydride transfers see: Sorensen, T. S.; Whitworth, S. M. *J. Am. Chem. Soc.* **1990**, *112*, 6647-6651.
11. This conformation would likely have the ethyl group in an axial orientation due to $A^{1,2}$ strain (Hoffmann, R.W. *Chem. Rev.*, **1989**, *89*, 1841-1860.

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