

Communications

Unexpected Anti-Markovnikov Addition to 1-Methoxy-1,3-cyclohexadiene

Sadie L. Emery, Carmen H. Fies, Evan J. Hester, and John V. McClusky*

Division of Earth and Physical Sciences, The University of Texas at San Antonio, 6900 North Loop 1604 West, San Antonio, Texas 78249

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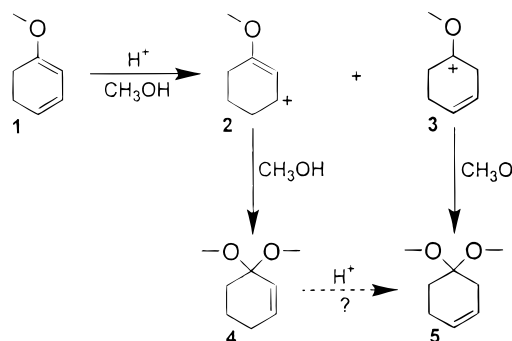
The concepts of carbocation stability and resonance stabilization are central tenets in organic chemistry, and much regiochemistry can be explained in terms of formation of the more stable carbocationic intermediate. Thus Markovnikov addition and the role of carbon substitution on S_N1 and $E1$ chemistry are promptly taught to first year organic chemistry students.

We have noticed an unusual reaction of 1-methoxy-1,3-cyclohexadiene, **1**, in methanol with catalytic *p*-toluenesulfonic acid.¹ Isolation of the major product by gas chromatography and identification by 1- and 2-dimensional NMR spectroscopy and comparison with literature demonstrated that the major product was the dimethyl ketal of cyclohexa-3-enone, **5**.² The direct formation of this product involves protonation to form the *less* stable cation **3**, followed by capture of the cation by the methanol solvent, Scheme 1. The cationic precursor to **5** is stabilized only through resonance with the ether oxygen, while protonation at carbon 4 of **1** would have generated a carbocation **2** which was stabilized by both the ether oxygen and the adjacent double bond. On the basis of simple resonance theory, the observed product appears to be formed from the *less* stable cation. We have explored this reaction in further detail to determine the cause of this unexpected regiochemistry.

We have investigated the relative stability of the di-conjugated cation intermediate **2** and the mono-conjugated intermediate cation **3** by ab initio theory using the Gaussian 98 program.³ Even at the MP2//6-31G(d) and B3LYP/6-31G(d)//B3LYP/6-31G(d) levels of theory, the di-conjugated cation is more stable than the mono-conjugated cation by approximately 14 kcal/mol, Table 1. This energy difference should completely eliminate the formation of product **5** by a direct mechanism.

It is conceivable, however, that the reaction proceeds through the more stable cation **2** and then undergoes a rapid rearrangement under the acidic conditions to form the observed product. We have therefore calculated the relative energies of the two ketals **4** and **5**, Table 1. Again, several levels of theory predict that the observed ketal is indeed the more stable isomer. This difference, however, is slight: approximately 0.6 kcal/mol. Assuming complete equilibra-

Scheme 1



tion, one would expect a product ratio of approximately 70:30; however, none of the conjugated ketal **4** is observed. Were the actual energy difference 1.7 kcal/mol (a typical uncertainty for such calculations), the expected product ratio would be 95:5. This obviously does not rule out an equilibrium process.

Kinetics and labeling studies are often valuable tools for differentiating between alternative reaction mechanisms. Thus we have followed this reaction by 500 MHz NMR in methanol- d_4 . These experiments demonstrated that any rearrangement from **4** to **5** must occur very rapidly, as no new products or intermediates were observed during the reaction (Scheme 1). More importantly, the position of deuterium incorporation is a strong indication of the pathway for formation of product **5** (Scheme 2). Formation of the more stable cation **2** would have incorporated deuterium on carbon 4, while generation of the less stable mono-conjugated cation **3** would have incorporated deuterium on carbon 2. Experimentally, deuteration was observed only on carbon 2 of the product **5**. This is consistent with direct formation of **5** from **3**. Acid-catalyzed rearrangement of **4** to **5** can be eliminated since the product **5** would have a minimum of 50% deuterium incorporation at carbon 4. Therefore, this experiment rules out formation of the more stable di-conjugated cation **2** followed by a subsequent rearrangement to the observed product **5**.

So why does the reaction proceed through the less stable intermediate **3**? One might initially expect protonation of carbon 2 of the diene **1** to be analogous to conjugated enolate alkylation chemistry. Indeed, calculations indicate that carbon 2 has the highest electron density of all the alkene carbons. However, the Hammond postulate suggests that this analogy should not hold. Enolate alkylation begins with a high-energy starting material and forms a lower energy product; thus, the transition state should be early and mimic the starting enolate. The reverse is true for the addition of a proton to **1**; here a lower energy starting material is converted into a high-energy intermediate. The transition state mirrors the cation, and the 14 kcal/mol difference in cation energies should be reflected in the activation energies for the two reactions. Therefore, electron populations of the starting diene cannot explain the observed product from this reaction.

Similar arguments can eliminate a mechanism involving anchimeric assistance whereby the proton is delivered to carbon 2 of **1** by a methanol molecule hydrogen bonded to the ether oxygen. These interactions, while favoring the observed protonation, do little to change the relative stability of the transition states.

* To whom correspondence should be addressed. Phone: (210) 458-5454. Fax: (210) 458-4469. E-mail: jmclclusky@utsa.edu.

(1) In a typical experiment 10 mg of **1** (purified by preparative gas chromatography) was dissolved in 0.6 mL of dry methanol- d_4 , and approximately 0.1 mg of *p*-toluenesulfonic acid was added. The reaction was followed by NMR and/or GC (15 m DB-1 megabore column). The reaction was quenched by the addition of excess sodium bicarbonate. No change in the product mixture was observed following addition of the base.

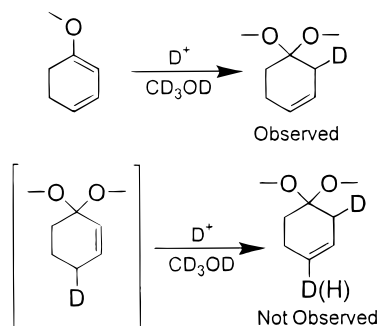
(2) The product was identical to independently synthesized material according to published procedures: Lambert, J. B.; Xue, L.; Bosch, R. J.; Taba, K. M.; Marco, D. E.; Urano, S.; LeBreton, R. R. *J. Am. Chem. Soc.* **1986**, *108*, 7575.

(3) Gaussian 98W (Version 5.0), M. J. Frish, et al., Gaussian, Inc., Pittsburgh, PA 1998.

Table 1. Ab Initio Energies (kcal/mol) of Cationic Intermediates and Final Products

| species | 6-31G(d)//6-31G(d) | B3LYP/6-31G(d)//B3LYP/6-31G(d) | MP2//6-31G(d) | B3LYP/6-31G(d)//B3LYP/6-31G(d) methanol dielectric |
|----------|--------------------|--------------------------------|---------------|---|
| 2 | 0 | 0 | 0 | 0 |
| 3 | +13.0 | +13.44 | +14.3 | +11.2 |
| 4 | +0.60 | +0.38 | +0.76 | |
| 5 | 0 | 0 | 0 | |

Scheme 2



However, it is possible that in methanol solvent a free carbocation is never formed. Rather, the nascent cation may be captured by the solvent as soon as protonation begins in an Ad_E3 (addition, electrophilic, termolecular) type mechanism.⁴ This mechanism is essentially the reverse of an $E2$ elimination. Since the cation would not be fully formed, the differences in energy between the two possible cations could be significantly less than for the fully developed intermediates. In addition, this would minimize the stabilizing effect of the additional resonance structure. However, it is unlikely that this is the sole cause of the unexpected product. Ad_E3 chemistry is most commonly observed during formation of unstabilized secondary cations, unlike **2** or **3**.⁴ Also if one assumes that the transition state for each reaction occurs at the same position along the reaction coordinate, then the transition state leading to **2** would still be lower in energy than that for **3**. Only by having the transition states at different positions—that for **3** being earlier than that for **2**—can the Ad_E3 mechanism explain the observations. Given the similarities between the two pathways, this is unlikely.

(4) See for example: Fahey, R. C.; Monahan, M. W.; McPherson, C. A. *J. Am. Chem. Soc.* **1970**, *92*, 2810. Fahey, R. C.; Monahan, M. W. *J. Am. Chem. Soc.* **1970**, *92*, 2816.

Standard ab initio calculations are representative of the carbocations in the gas phase; however, the methanol solvent can strongly affect the energies of such charged intermediates. We have completed the calculations using self-consistent isodensity polarized continuum model (SCI-PCM)⁵ at the B3LYP/6-31G(d)//B3LYP/6-31G(d) level. In this model, a hole is placed in the continuum solvent dielectric field (that for methanol was used), and the molecule is placed into this hole. The interactions between the molecule and continuum solvent are optimized throughout the calculation. These calculations include the stabilizing dipolar interactions between the cation and methanol but leave out any specific intermolecular interactions. As can be seen in Table 1, the unconjugated cation is still disfavored by over 11 kcal/mol. We therefore conclude that specific intermolecular interactions between solvent and reactant play a crucial role in determining the outcome of this reaction. Since methanol is small and very polar, it can easily coordinate and stabilize the incipient cation. Differences between the coordination complexes for **2** and **3** may reverse their expected stabilities and thereby the reaction products. This is the working hypothesis for our continuing explorations into this fascinating reaction.

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Supporting Information Available: Experimental details and 1H NMR, ^{13}C NMR, and 1H COSY of deuterated product **5** purified by preparative gas chromatography. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO9824495

(5) Foresman, J. B.; Keith, T. A.; Wiberg, K. B.; Snoonian, J.; Frisch, M. J. *J. Phys. Chem.* **1996**, *100*, 16098.