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Isotope effects and the mechanism of deoxygenation of epoxides with dichlorocarbene

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Abstract—The deoxygenation of styrene oxide with dichlorocarbene is studied by a combination of isotope effects and theoretical calculations. A normal ¹³C isotope effect of 1.016 is observed for the α -carbon of the styrene oxide but a surprising inverse isotope effect of 0.995 is observed at the β -carbon. This is indicative of a highly asynchronous process in which the C_{α} —O bond is broken without any progress in the breakage of C_{β} —O bond. Theoretical calculations support this interpretation. This coarctate reaction is formally concerted as it avoids involving a high-energy intermediate, but it appears uninfluenced by transition state aromaticity. © 2005 Published by Elsevier Ltd.

Coarctate reactions are those in which two bonds are simultaneously formed and broken at an atom.¹ A surprisingly large number of reactions involve transformations that are formally coarctate processes—in fact about 2% of organic reactions based on a computerized search.² A theory of coarctate transition states has been described, based on a topological transformation of the Dewar/Zimmerman concept of transition state aromaticity.¹

In our view the most chemically interesting question for coarctate reactions is the degree to which concert is favored by transition state aromaticity. What portion of the large number of formally coarctate reactions are in fact concerted processes? If they are concerted, is there a stabilization of synchronous bonding transformations, or do the reactions involve highly asynchronous bonding changes, with concertness only being a way of avoiding high-energy intermediates? We have initiated an experimental and computational examination of coarctate reactions with the goal of addressing these questions. We describe here our results with one very simple coarctate reaction—the deoxygenation of epoxides with carbenes.

The deoxygenation of epoxides with carbenes has often been observed but it is complicated by the further reac-

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tivity of the product alkene.^{3–6} As a result, the yield of alkene from these reactions is typically low. However, the deoxygenation itself appears to be both facile and clean. The reaction is stereospecific, retaining the *cis* or *trans* stereochemistry of the original epoxide.^{5,6} Ylide intermediates (i.e., **1**) have often been proposed in these reactions,^{3,5,6} but an attempt to observe such an ylide was not successful.⁵

$$> 0 + :CX_2 \longrightarrow 0 = CX_2 + \| \xrightarrow{:CX_2} [CX_2]$$

$$[\bigcirc \stackrel{+}{O} - \stackrel{-}{C}X_2]$$

Our goals in applying kinetic isotope effects (KIEs) to study these reactions were to distinguish rate-limiting formation of an ylide versus a rate-limiting deoxygenation process, and to use the KIEs as a gauge of the asynchronicity of the breaking of the two C–O bonds. The latter goal requires the use of an unsymmetrically substituted epoxide, as a symmetrical epoxide will lead to symmetrical isotope effects due to averaging. The deoxygenation of styrene oxide (2) with dichlorocarbene was chosen for study.



Keywords: Isotope effects; Mechanism; Deoxygenation; Epoxide; Coarctate.

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Previous deoxygenation of 2 using phase-transfer/emulsifying conditions had been plagued by the side reaction of basic hydrolysis of the epoxide.⁶ The use of solid KOH, with no discrete aqueous phase, and 18-crown-6 as the phase transfer catalyst appears to alleviate this problem. Under these conditions, no phenylethylene glycol could be observed, and the formation of 3 was nearly quantitative based on NMR analysis versus an internal standard.

The ¹³C KIEs for deoxygenation of **2** were studied by NMR methodology at natural abundance.⁷ A total of four reactions of **2** at 40 °C were taken to 72–82% conversion, and the starting **2** was recovered by an aqueous workup followed by flash chromatography and microdistillation. The ¹³C NMR of the samples of recovered **2** was analyzed along with standard samples that had not been subjected to the reaction conditions. The change in isotopic composition in each position was determined relative to the *para* aromatic carbon, with the assumption that isotopic fractionation of this carbon was negligible. From the percentage conversions and the changes in isotopic composition, the KIEs were calculated as previously described.⁷

Figure 1a shows the average KIEs from the four independent determinations. A substantial normal (>1) ¹³C KIE was observed at the epoxide carbon adjacent to the aromatic ring (C_{α}). In contrast, the KIE at the distal carbon (C_{β}) is surprisingly inverse (<1). The KIEs for the aromatic ring carbons are within experimental error of unity.

If the deoxygenation involved rate-limiting formation of an epoxide-carbene ylide complex, the C_{α} and C_{β}^{13} C KIEs would be near unity. The observation of a substantial C_{α} KIE rules this out—an ylide may still be involved but it is not kinetically important. The standard qualitative interpretation of the $C_{\alpha}\ KIE$ is that the C_{α} -O bond is being broken in the rate-limiting step. However, the inverse C_{β} -KIE suggests that the C_{β} -O bond has gotten stronger at the transition state than it was in the starting material. Together, these results are indicative of a transition state that would be best described as a ring-opening process rather than a synchronous deoxygenation. This does not rule out a formally concerted deoxygenation, but the two C-O bonds are clearly breaking in different stages of the process.



Figure 1. (a) Experimental ¹³C KIEs (k_{12C}/k_{13C}) for the deoxygenation of styrene oxide at 40 °C. Standard deviations in the last digit from four determinations are shown in parentheses. (b) Predicted ¹³C KIEs based on transition structure **4**.

Theoretical calculations were used to interpret these results in greater detail. The deoxygenation of 2 with dichlorocarbene was studied in B3LYP calculations employing a 6-311++G(2d,p) basis set. Three transition structures were located, two with the carbene attacking the epoxide oxygen anti to the phenyl group and one syn to the phenyl group. The best of these structures (4) is 5.5 kcal/mol (including zpe) above separate starting materials. Structure 4 notably places the lone pair of the carbene moiety *anti* to the breaking C_{α} -O bond. This is favored by 4.3 kcal/mol over the second best structure (given in Supplementary data) in which the carbene lone pair is syn to the breaking C_{α} -O bond. Similar results were obtained in B3LYP, mPW1PW91 and MP2 calculations employing smaller basis sets, as described in Supplementary data.



As expected from the isotope effects, transition structure **4** is undergoing cleavage of the C_{α} –O bond but not the C_{β} –O bond. To test the consistency of this transition structure with the experimental isotope effects, the KIEs for **4** were predicted from the scaled theoretical vibrational frequencies⁸ using conventional transition state theory by the method of Bigeleisen and Mayer.⁹ Tunneling corrections were applied using the one-dimensional infinite parabolic barrier model.¹⁰ Such KIE predictions including a one-dimensional tunneling correction have proven highly accurate in reactions not involving hydrogen transfer, so long as the calculation accurately depicts the mechanism and transition state geometry.¹¹

The results are shown in Figure 1b. It is apparent that the predicted KIEs are quite similar in pattern to those observed experimentally. This supports the qualitative interpretation of the isotope effects and the approximate accuracy of 4. Since some degree of charge buildup at the transition state would be stabilized in solution, the gas phase structure 4 cannot be expected to be perfectly accurate. Considering this limitation of the calculations, the agreement between predicted and experimental KIEs is in fact very good.

No stationary point corresponding to an ylide geometry could be located in these calculations. A very loose epoxide– CCl_2 complex with an O–C distance of 2.60 Å was found on the potential energy surface, but the en-

ergy of this complex is only 1.6 kcal/mol below separate reactants and its free energy is 7.2 kcal/mol above reactants at standard state. Such a complex is unlikely to be a minimum on the free-energy surface and is mechanistically irrelevant.

When the steepest–descent reaction path in mass-weight coordinates is followed onward from 4, the C_{α} –O bond distance increases rapidly to >2 Å while the C_{β} –O distance at first stays below 1.5 Å. However, there is ultimately no barrier to dissociation of the products, phosgene and styrene, which are downhill from 4 by 86.8 kcal/mol, so the C_{β} –O bond breaks without there being an intermediate. The deoxygenation is thus overall a formally concerted process.

The picture that emerges from these results may be understood with reference to a More O'Ferrall-Jencks diagram¹² for the deoxygenation (Fig. 2). The transition state is early and breakage of the two C-O bonds is highly asynchronous. The reaction path starts out in a direction that would lead to the intermediate at the adjacent corner of the diagram. However, some time after the transition state, the reaction path avoids the high-energy intermediate (either a diradical or a zwitterion) by curving toward the extremely stable products. We note that if a synchronous coarctate transition state were substantially stabilized by transition state aromaticity, the reaction path would be expected to pass in some degree toward the middle of the More O'Ferrall-Jencks diagram. Based on the isotope effects and the calculational predictions, this is not the case.

Would this highly asynchronous pathway apply to a symmetrical epoxide? As described above, this question cannot be addressed well experimentally with isotope effects. However, calculations suggest that the preference for an asynchronous pathway is general. Transition structure **5** was located for the deoxygenation of *cis*-2,3-dimethyloxirane in B3LYP/6-311++G(2d,p) calculations. The barrier in this reaction is predicted to be 6.2, 0.7 kcal/mol higher than with **2**. The transition structure is somewhat later, but it is still very early. As was true in **4**, **5** places the lone pair of the carbene moiety *anti* to the



Figure 2. More O'Ferrall–Jencks diagram for the deoxygenation of styrene oxide with dichlorocarbene.

breaking C–O bond. This arrangement is reminiscent of the anomeric effect and may be viewed as maximizing overlap between the lone pair and the σ^* orbital of the breaking C–O bond, stabilizing the transition state. An alternative transition structure in which the lone pair is *syn* to the breaking bond (Supplementary data) was 9.5 kcal/mol higher in energy. The stabilizing effect of the *anti* lone pair appears to enforce asynchronicity in the reaction, as the lone pair can only aid in breaking one of the two C–O bonds.



Dewar has pointed out that there is an intrinsic preference for reactions to avoid synchronous bonding changes.¹³ This preference may be overcome by special factors in transition states, most particularly transition state aromaticity for pericyclic reactions. The degree to which transition state aromaticity aids synchronicity in coarctate reactions remains to be seen. For the deoxygenation of epoxides with carbenes, it appears that the preference for asynchronous bonding changes wins out. Among coarctate reactions, deoxygenation may not be typical-its high exothermicity and resulting early transition state make it arguably non-ideal for observing any special stabilization of a synchronous transition state—but for this coarctate reaction at least, there is no apparent influence of transition state aromaticity.

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Supplementary data

Experimental procedures, NMR integration results, calculational procedures, and energies and geometries of all calculated structures. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.01.153.

References and notes

1. Herges, R. Angew. Chem., Int. Ed. Engl. 1994, 33, 255–276.

- 2. Herges, R. J. Chem. Comput. Sci. 1994, 34, 91-102.
- Nozaki, H.; Takaya, H.; Noyori, R. *Tetrahedron* 1966, 22, 3393–3401; Halton, B.; Russell, S. G. G. J. Org. Chem. 1991, 56, 5553–5556.
- Wittig, G.; Schlosser, M. Tetrahedron 1962, 18, 1023– 1028; Mannfov, G. G.; Berdnikov, E. A.; Samuilov, Y. D. Russ. J. Org. Chem. 2001, 37, 339–344.
- 5. Shields, C. J.; Schuster, G. B. Tetrahedron Lett. 1987, 28, 853–856.
- Tabushi, I.; Kuroda, Y.; Yoshida, Z. Tetrahedron 1976, 32, 997–1000.
- Singleton, D. A.; Thomas, A. A. J. Am. Chem. Soc. 1995, 117, 9357–9358.
- The calculations used the program QUIVER Saunders, M.; Laidig, K. E.; Wolfsberg, M. J. Am. Chem. Soc. 1989, 111, 8989–8994, Becke3LYP frequencies were scaled by 0.9614.

- (a) Bigeleisen, J.; Mayer, M. G. J. Chem. Phys. 1947, 15, 261–267; (b) Wolfsberg, M. Acc. Chem. Res. 1972, 5, 225– 233; (c) Bigeleisen, J. J. Chem. Phys. 1949, 17, 675– 678.
- 10. Bell, R. P. *The Tunnel Effect in Chemistry*; Chapman & Hall: London, 1980; pp 60–63.
- (a) Beno, B. R.; Houk, K. N.; Singleton, D. A. J. Am. Chem. Soc. 1996, 118, 9984–9985; (b) Meyer, M. P.; DelMonte, A. J.; Singleton, D. A. J. Am. Chem. Soc. 1999, 121, 10865–10874; (c) DelMonte, A. J.; Haller, J.; Houk, K. N.; Sharpless, K. B.; Singleton, D. A.; Straßner, T.; Thomas, A. A. J. Am. Chem. Soc. 1997, 119, 9907–9908; (d) Singleton, D. A.; Merrigan, S. R.; Liu, J.; Houk, K. N. J. Am. Chem. Soc. 1997, 119, 3385–3386.
- More O'Ferrall, R. A. J. Chem. Soc. B 1970, 274; Jencks, W. P. Chem. Rev. 1972, 72, 705.
- 13. Dewar, M. J. S. J. Am. Chem. Soc. 1984, 106, 209-219.