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Isotope effects and the mechanism of fragmentation of epoxy imino-1,3,4-oxadiazolines

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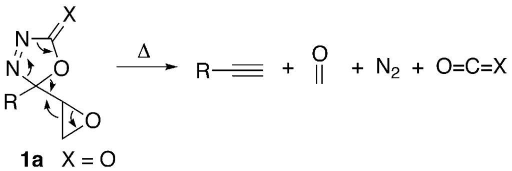
Abstract—The fragmentation of an epoxy imino-1,3,4-oxadiazoline is studied by a combination of isotope effects and theoretical calculations. Significant primary ^{13}C isotope effects are observed at the two oxadiazoline carbons but negligible isotope effects are observed at the remaining carbons. This is consistent with a rate-limiting fragmentation of the oxadiazoline without fragmentation of the adjacent epoxide ring. Theoretical calculations support this interpretation. This formal coarctate reaction avoids two complicated coarctate fragmentations in favor of a multi-step mechanism with a simple coarctate final step.

Many organic transformations involve multiple complicated bonding changes. In depicting the mechanism for such reactions, it is often tempting for organic chemists to describe the changes as occurring in a concerted fashion. A one-step mechanism not only confers simplification; it also avoids an often difficult decision as to which bonds are made or broken first and which intermediates are involved. However, the individual bonding changes occurring in a transition state will each have an associated energy cost;[1] if too many bonds are made or broken at once, the barrier becomes prohibitive. It was for this reason that Dewar concluded that, with significant exceptions, 'multibond reactions cannot normally be synchronous'.[2] This does not exclude formally concerted reactions in which bonding changes occur in different 'stages', but when low-energy intermediates are available, reactions tend to prefer multi-step mechanisms. The most notable exceptions to this rule are pericyclic reactions, in which transition state aromaticity can counteract the cost of simultaneous bonding changes.

The intriguing thermolytic fragmentations of the Δ^3-1,3,4-oxadiazolin-2-ones (**1a**) and 2-imino-Δ^3-1,3,4-oxadiazolines (**1b**) derived from α,β-epoxyketones break a total of five σ-bonds in the starting material to afford five new π-bonds in the products.[3] From the shear complexity of these transformations, one might normally expect a multi-step mechanism. However, a special aspect of these reactions can be argued to favor a concerted fragmentation. Herges has analyzed these fragmentations within the framework of 'coarctate' reactions.[4] Coarctate reactions are those in which two bonds are simultaneously formed and broken at an atom, and are thought to constitute about 2% of organic reactions.[5] A concerted coarctate reaction can be analyzed as a topological transformation of a pericyclic reaction, and a coarctate transition state can be stabilized by transition state aromaticity. Herges concluded that a concerted coarctate fragmentation of **1a**/**1b** was operative and accounted for experimental reactivity observations.[4]



1a X = O
1b X = NR'

An important fundamental question is whether the transition state aromaticity of a coarctate reaction is sufficient to overcome the opposing intrinsic preference for a multi-step mechanism. We have, therefore, carried out a combined experimental and theoretical

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Keywords: Isotope effects; Mechanism; Fragmentation; Coarctate.

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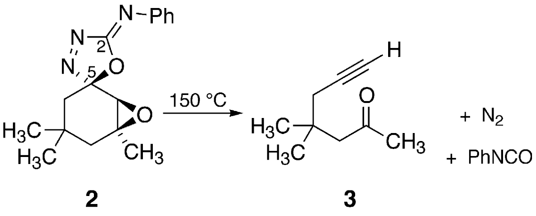
study of the fragmentation of an epoxy 2-imino-1,3,4-oxadiazoline. The results implicate a multistep mechanism with a relatively simple coarctate last step.

The 2-phenylimino-Δ^3-1,3,4-oxadiazoline **2** derived from isophorone oxide was chosen for study because it was previously found to afford relatively high yields of fragmentation products.[3] A significant complication with this molecule, however, is that its synthesis by oxidation of the semicarbazone of isophorone oxide affords an approximately 2:1 mixture of diastereomers. The minor isomer was found to interfere with the determination of kinetic isotope effects (KIEs) below, so that **2** had to be purified by a tedious chromatography. This limited the scale at which **2** could be studied, negatively affecting the precision of the KIEs obtained. The stereochemistry of the major isomer **2** was verified by X-ray crystallography.



The ^{13}C KIEs for fragmentation of **2** were determined combinatorially by NMR methodology at natural abundance.[6] Three reactions of **2** in diphenyl ether at 145–150 °C were taken to 65%, 70%, and 84% conversion, and the starting **2** was recovered by flash chromatography followed by recrystallization (CH_2Cl_2/hexanes). The samples of recovered **2** were analyzed by ^{13}C NMR, 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 carbon of the methyl substituent on the epoxide ring,[7] 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.[6]

Figure 1a shows the average KIEs from the three independent determinations. The uncertainties in the KIEs are larger than normal, due to the limited scale and limited solubility of **2** in NMR determinations. Nonetheless, the KIEs end up acceptably reliable in their basic observations. Significant ^{13}C KIEs were observed in the C-2 and C-5 ring carbons of the 1,3,4-oxadiazoline, and their magnitude is consistent with a primary carbon KIE. This suggests that these carbons are undergoing a σ-bonding change in the transition state for the rate-limiting step. In contrast, the remaining KIEs are smaller, mainly within experimental error of unity. The absence of a significant ^{13}C KIE at the quaternary epoxide carbon in particular suggests that the epoxide ring is not undergoing fragmentation in the rate-limiting step. Overall, these KIEs qualitatively support a transition state in which the 1,3,4-oxadiazoline is fragmenting but not the remainder of the molecule.

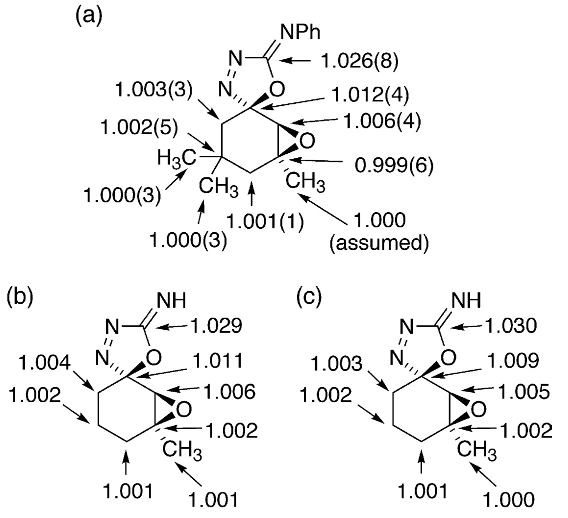
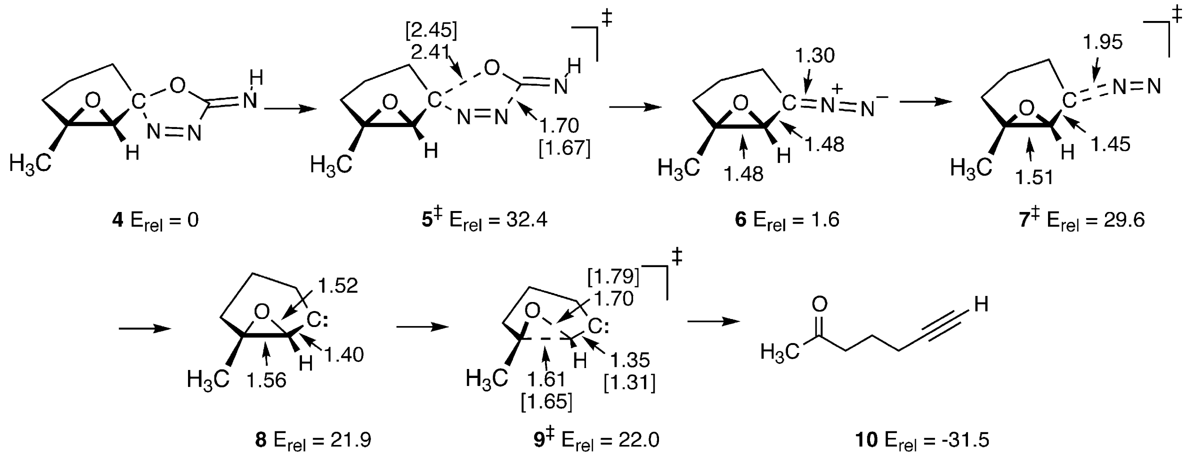


Figure 1. (a) Experimental ^{13}C KIEs (k_{12C}/k_{13C}) for the fragmentation of **2** at 145-150 °C. Standard deviations from three independent determinations are shown in parentheses. (b) Predicted ^{13}C KIEs based on the mPW1K/6-31+G(d,p) version of transition structure **5**. (c) Predicted ^{13}C KIEs based on the B3LYP/6-31+G(d,p) version transition structure **5**.

Theoretical calculations were used to interpret these results in greater detail and to explore the complete reaction mechanism. The fragmentation of the calculational model **4** was explored in both B3LYP and mPW1K[8] calculations, employing a 6-31G* basis set to survey the potential energy surface and reoptimizing important stationary points with a 6-31+G(d,p) basis set (Fig. 2).

Extensive efforts failed to locate a transition structure that directly affords the ultimate product **3**. Instead, two fragmentation processes were identified, and because of two distinct conformations in the 6-membered ring, a total of four fragmentation transition structures were located. We will consider only the lowest-energy conformation for each process—higher energy alternative transition structures are given in the Supplementary data.

The calculationally favored fragmentation affords the diazo epoxide **6** and isocyanic acid via transition structure **5**. The predicted barrier is 32.4 kcal/mol (B3LYP/6-31+G(d,p)+zpe), which is well consistent with a unimolecular reaction that occurs over the course of about an hour at 150 °C. The mPW1K-predicted barrier for fragmentation via **5** is 44.4 kcal/mol. This is too high; since this fragmentation may be viewed as a pericyclic process (a retro 1,3-dipolar cycloaddition) and since RHF calculations greatly overpredict the barrier for pericyclic reactions, it may be that the hybrid mPW1K calculation[8] mixes in too much RHF character for an accurate barrier prediction in this reaction.

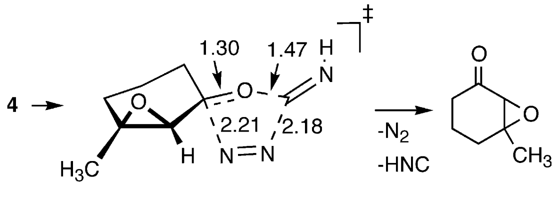


4 $E_{rel} = 0$ **5**‡ $E_{rel} = 32.4$ **6** $E_{rel} = 1.6$ **7**‡ $E_{rel} = 29.6$

8 $E_{rel} = 21.9$ **9**‡ $E_{rel} = 22.0$ **10** $E_{rel} = -31.5$

Figure 2. Predicted mechanism for the fragmentation of computational model **4**. Relative energies (B3LYP/6-31+G(d,p)+zpe) are shown in kcal/mol and select distances are shown in Å. Distance in brackets refer to structures located in mPW1K/6-31+G(d,p) calculations.

The alternative fragmentation process located affords an epoxy ketone (**12**), N_2, and hydrogen isocyanide via transition structure **11**. The barrier in this case is predicted to be 3.6 kcal/mol higher than the barrier for formation of the diazo epoxide **6**. It should be noted that this alternative fragmentation is known to occur in some similar reactants.[3]



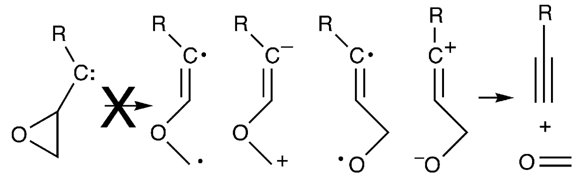
11‡ $E_{rel} = 36.0$ **12**

The experimental relevance of transition structure **5** was gauged by comparison of predicted isotope effects based on **5** with the experimental KIEs. The KIEs for **5** were predicted from the scaled theoretical vibrational frequencies[9] using conventional transition state theory by the method of Bigeleisen and Mayer.[10] Tunneling corrections were applied using the one-dimensional infinite parabolic barrier model.[11] 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.[12]

The results for the mPW1K and B3LYP versions of **5** are shown in Figure 1b and c, respectively. It is apparent that the predicted KIEs are quite similar in pattern to those observed experimentally. Considering this limited precision of the experimental KIEs, the agreement between predicted and experimental KIEs is in fact excellent. This supports the qualitative interpretation of the isotope effects above and the approximate accuracy of **5**. Little difference is seen between the mPW1K and B3LYP predictions, and one cannot tell which transition structure geometry is more accurate.

The remainder of the reaction mechanism for the calculational model involves the conversion of diazo epoxide **6** into heptynone **10**. This conversion itself could potentially occur by a concerted coarctate process in which loss of the N_2 is accompanied by fragmentation of the epoxide. Instead, the calculations predict a two-step mechanism in which **6** first loses N_2 via transition structure **7** to afford carbene **8** and then **8** fragments via transition structure **9** to afford **10**. Although no concerted transition structure for conversion of **6** to **10** could be located, it should be noted that the barrier for the second step on the B3LYP surface is predicted to be very low–only about 0.15 kcal/mol. Under these circumstances, a very small error in the potential energy surface can make the difference between stepwise and concerted mechanisms. The mPW1K mechanism more strongly favors the stepwise process, as the barrier for fragmentation of **8** goes up to 5.5 kcal/mol. High-level single-point energies (CCSD(T)/6-31 + G(d,p)//B3LYP/6-31 + G(d,p)) predict an even larger barrier of 14.0 kcal/mol for fragmentation of **8**.[13] This large spread in the theoretical predictions is disconcerting but none of the calculations support a concerted coarctate conversion of **6** to **10**. Unfortunately the experimental KIEs can have no bearing on this issue.

In the conversion of **8** to **10**, the α-epoxide carbon is transformed into the terminal acetylenic carbon, breaking two σ-bonds and forming two new π-bonds. Thus, this is a concerted coarctate reaction in itself. Alternative two-step mechanisms may be considered for this conversion, as in the fragmentation of **13** via **14**–**17**, but in each case the intermediate would expectantly be very high in energy. Because of this, such a very simple coarctate reaction has no choice but to proceed by a concerted mechanism. This does not tell us anything about the degree to which transition state aromaticity stabilizes the coarctate transition state.



13 **14** **15** **16** **17**

In summary, the theoretically predicted and KIE-supported mechanism for these reactions must three times face a choice between a concerted coarctate reaction and multi-step process. At the stage of **4**, where the concerted reaction would be very complicated, the stepwise process is favored. At the stage of the diazo epoxide **6**, the stepwise process again appears to be favored. The preference for a stepwise mechanism going on from **6** is less pronounced and less certain, but there is still no sign of a transition state aromaticity effect favoring a concerted coarctate process. The last step in the mechanism, going on from **8**, is a concerted coarctate reaction, but this may be viewed as being enforced by the necessity to avoid high-energy intermediates. Overall, the example here does not appear to demonstrate any special stabilization in coarctate transition states.

Acknowledgements

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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.2004.12.008.

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