Pergamon

Tetrahedron Letters 40 (1999) 639–642

TETRAHEDRON
LETTERS

Stereochemical Labeling at Natural Abundance. Stereochemistry, Isotope Effects, and Mechanism of the Diels-Alder Reaction of Hexachlorocyclopentadiene with Ethyl Vinyl Ether

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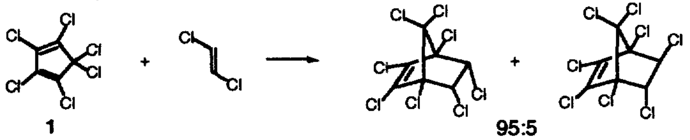
Received 12 November 1998; accepted 16 November 1998

Abstract: The variation in cis versus trans deuterium content in natural-abundance ethyl vinyl ether is retained in its cycloadduct with hexachlorocyclopentadiene, indicative of a stereospecific process. The kinetic isotope effects for this reaction were also determined at natural abundance, and suggest a very asynchronous but concerted process. This conclusion is backed by comparison with theoretically calculated isotope effects. © 1999 Elsevier Science Ltd. All rights reserved.

The stereochemistry of addition reactions or cycloadditions of alkenes is a fundamental mechanistic probe. Stereospecificity in additions or cycloadditions is defined by the formation of diastereomeric products from diastereomeric starting materials - usually cis-trans isomers for alkenes. A lack of stereospecificity is generally indicative of a stepwise addition, while a stereospecific syn or anti addition is supportive (but not proof) of concerted bond formation to the ends of an alkene. Such stereochemical studies have often involved the use of minimally substituted, isotopically labeled alkenes - avoiding complications in the mechanistic interpretation of results from more substituted alkenes or their non-suitability for the reaction of interest. We describe here a method for determining the stereochemistry of additions to simple alkenes without labeling the alkene, taking advantage of the "natural" positional variation in deuterium content. This is exemplified by the Diels-Alder reaction of hexachlorocyclopentadiene with ethyl vinyl ether, in which both the stereochemistry and a complete set of ^{13}C and ^{2}H kinetic isotope effects (KIEs) have been determined at natural abundance. The results, in combination with theoretically calculated isotope effects, provide insight into the reaction mechanism.

While stepwise processes have been established in a few cases,[1-3] it is generally agreed that most Diels-Alder reactions occur by concerted mechanisms. However, for some important classes of Diels-Alder reactions the mechanism is still unclear. An example is the reaction of hexachlorocyclopentadiene (**1**) with electron-rich alkenes, often considered typical examples of "inverse electron demand" Diels-Alder reactions. The cycloaddition of **1** with *electron-poor* alkenes is well understood to involve a stepwise process, based on a lack of stereospecificity.[3] For example, the reaction of **1** with trans-1,2-dichloroethylene (eq 1) affords mainly the *cis* adduct. On the other hand, the reaction of **1** with electron-rich alkenes is *usually* stereospecific: reactions with *trans*-2-butene[3] and β-deuterated-α-methylstyrene[4] are stereospecific, but *trans*-β-methylstyrene and *trans*-stilbene each afford significant amounts of the cis cycloadduct.[3] The variability of stereochemical results in these reactions has made it particularly difficult to decide whether stereospecificity, when observed, is the result of a concerted mechanism or a stepwise process in which the ring closure of a biradical intermediate is faster than loss of stereochemistry.[1]



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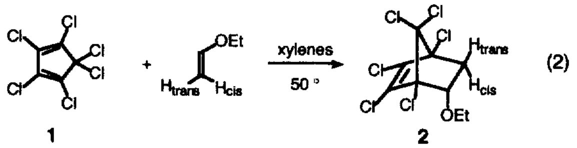
PII: S0040-4039(98)02508-8

The cycloaddition of **1** with ethyl vinyl ether was studied here because it is a true inverse electron demand reaction and occurs under much milder conditions than used in previous studies, affording the endo cycloadduct **2** in quantitative yield at 50 °C (eq 2).[5] Significant positional variation in isotopic composition is common and has been taken advantage of in studies of the origin of natural materials.[6] For mono-substituted alkenes the relative amount of deuterium trans versus cis to the substituent will depend upon its source. In the case of ethyl vinyl ether, the average ^{2}H NMR integration for the deuterium trans to the ethoxy group was 30.9% greater than that of the cis (Figure 1a) for a commercial bottle (Aldrich).[7] Complete conversion of a sample of this ethyl vinyl ether, using a large excess of **1** at 50 °C, afforded **2** which averaged 31.4% more deuterium trans to the ethoxy group than cis (Figure 2b). The standard deviation for multiple spectra was 1%, so that within experimental error the same excess of deuterium trans was observed in both the starting material and product. This is consistent with >97% stereospecificity in the reaction of both the trans and cis deuterated isotopomers of ethyl vinyl ether.[8]



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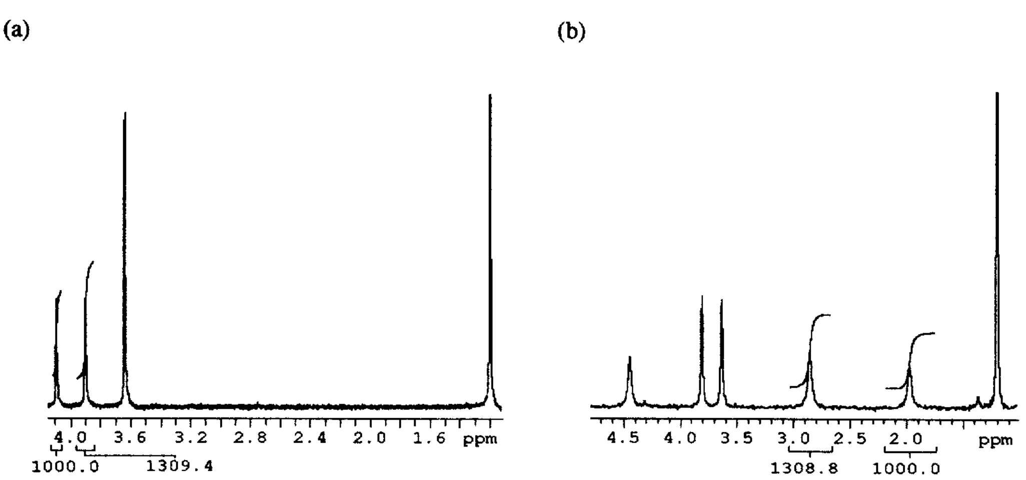
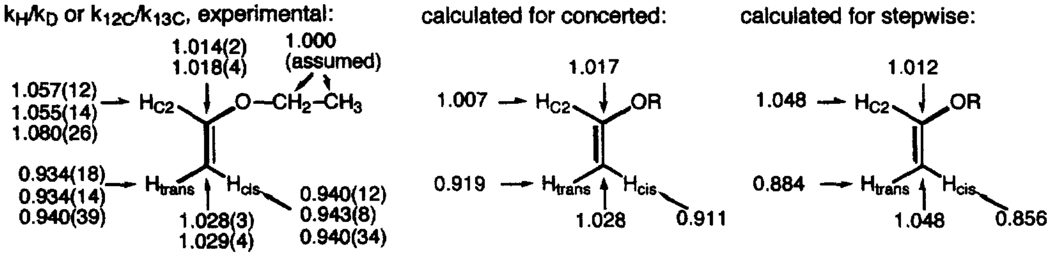


Figure 1. Expansions of the natural abundance ^{2}H NMR spectra of (a) ethyl vinyl ether and (b) **2**, derived from the same batch of ethyl vinyl ether. In (a), the deuteriums trans and cis to the ethoxy group are at δ 3.90 and 4.09, respectively. In (b), the deuteriums trans and cis to the ethoxy group are at δ 2.85 and 1.97, respectively.

The experimental KIEs for this reaction were determined by recently reported methodology for the combinatorial high-precision determination of ^{13}C and ^{2}H KIEs at natural abundance.[9] Reactions of natural abundance ethyl vinyl ether with **1** on a 2 mole scale were taken to 76.5, 80 and 80.5% (all ±2%) completion. The unreacted ethyl vinyl ether was recovered by a vacuum transfer followed by fractional distillation, and analyzed by ^{13}C and ^{2}H NMR[7] compared to a standard sample of original ethyl vinyl ether from the same bottle. The changes in ^{13}C and ^{2}H isotopic composition were calculated relative to the methyl ^{13}C peak and the methylene ^{2}H peak. (These peaks were chosen due to minimal complications from impurities.) From the changes in isotopic composition the KIEs and errors shown below were calculated as previously described.[9]

The qualitative interpretation of these results is that the significant ^{13}C and inverse ^{2}H KIEs for the terminal vinylic positions are indicative of significant bond formation to this center at the transition state. However, the degree of bonding to the internal olefinic carbon is much more difficult to define. Classically, the *normal* KIE at H_{C2} would be interpreted as indicating *no* bond formation to the internal carbon at the transition state, as rehybridization of this carbon toward sp^3 would be expected to lead to an inverse H_{C2} KIE. However, calculations and experimental models have suggested that the rehybridization model is far too simple; a true stepwise Diels-Alder reaction would be expected to exhibit a highly normal H_{C2} KIE due to a freer C-H bending vibration in the incipient radical.[10] A concerted but very highly asynchronous cycloaddition can also exhibit a moderately normal ^2H KIE at a center which ultimately becomes sp^3 hybridized.[11,10] Thus, the H_{C2} KIE of ≈1.06 cannot be definitively assigned to a stepwise or concerted process on a qualitative basis.



To aid in the interpretation of these results, the model Diels-Alder reaction of hydroxyethylene with 1 was investigated in (U)Becke3LYP calculations with a 6-31G* basis set. A transition structure for an asynchronous concerted Diels-Alder reaction was found in the (restricted) Becke3LYP calculations (Figure 2a), and a transition structure for the first step of a stepwise cycloaddition was found in unrestricted Becke3LYP calculations (Figure 2b). Attempts to locate additional stepwise structures involving other rotamers about the newly-forming bond were not successful.

Theoretical KIEs based on these transition structures were calculated as previously described.[12,13] In contrast to more successful KIE predictions in previous reactions,[14,12a] neither structure leads to an excellent prediction of the experimental KIEs. The ^{13}C KIEs predicted for the concerted transition state match very well with experiment, but the ^2H KIEs are underpredicted by 1-5%. The stepwise transition structure provides an excellent prediction for the critical H_{C2} KIE, but is far off in every other KIE.

The great difference between the predicted and experimental KIEs for all positions but H_{C2} makes a stepwise mechanism seem very unlikely. Our best interpretation of the experimental results is in terms of a concerted reaction with a transition state that is slightly more asynchronous than shown in Figure 2a. It is also possible that Figure 2a is fairly accurate but that H/D tunneling is underpredicted in our calculated KIEs. Either way, the observed stereospecificity of the reaction supports the conclusion of a concerted mechanism.

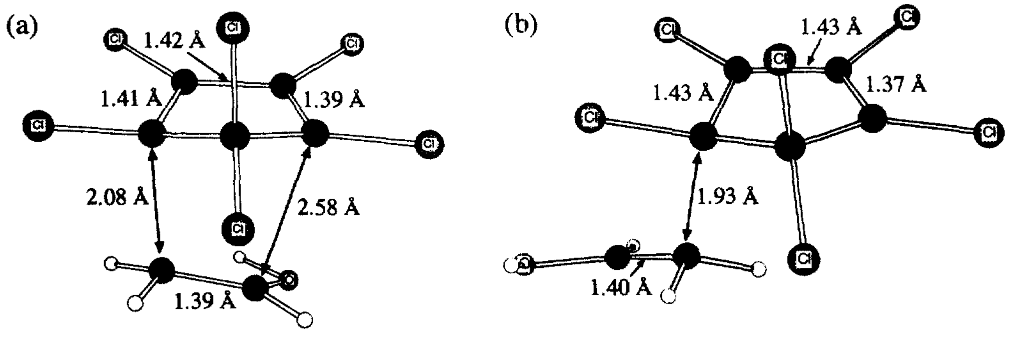


Figure 2. Transition structures predicted in (U)Becke3LYP/6-31G* calculations for an (a) concerted and (b) stepwise Diels-Alder reaction of 1 with hydroxyethylene.

We considered briefly the possibility of electron transfer or zwitterionic intermediates in these reactions. Becke3LYP/6-31G* calculations predict an inverse H_{C2} KIE of 0.979 and normal H_{cis} and H_{trans} KIEs of 1.019 and 1.037 for formation of the cation radical of hydroxyethylene, very different from the experimentally observed KIEs. In addition, no obvious rate change was noted when acetonitrile was used as solvent in place of xylenes. Thus, the intermediacy of highly charged species seems unlikely.

The trend in Diels-Alder reactions of **1** in going from stepwise to concerted reactions as the dienophile goes from electron poor to electron rich may be understood based on the changing facility of the concerted process. The rate of a concerted Diels-Alder reaction with **1** should increase greatly with increases in the HOMO energy of the dienophile, while the rate of a stepwise process should be dominated by the stability of the incipient diradical and won't necessarily be decreased for electron-poor alkenes. Thus, the concerted process can dominate for electron-rich alkenes and the stepwise process for electron-poor alkenes.

In addition to the determination of stereospecificity here, compounds which show a significant positional variation in ^{2}H or even ^{13}C composition[6b] should be useful in other kinds of classical physical organic labeling experiments. We are pursuing these possibilities.

Acknowledgment. We thank NIH grant # GM-45617 and The Robert A. Welch Foundation for support of this research.

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(7) A number of precautions were taken to minimize both random and systematic errors in the NMR analysis - see ref 9. Delays between pulses of $\approx$10 times the longest T_1 were used in spectra for the trans versus cis ^{2}H NMR integrations.

(8) (a) The excess deuterium trans in **2** would drop rapidly with incomplete stereospecificity. For example, if the stereochemistry of each isotopomer were retained in the product to the extent of only 95%, the excess deuterium trans in **2** would only be 27.5%, outside of experimental error. (b) In principle the excess deuterium trans in **2** could arise from a completely non-stereospecific process exhibiting a large isotope effect on product formation, but this seems very unlikely.

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(13) The calculated methylene-group k_H/k_D for the concerted reaction of 2,3-dichlorocyclopentadiene with ethyl vinyl ether (instead of hydroxyethylene) was 0.977. Since the experimental k_H/k_D's are *relative*[9] to the methylene group (used as standard), the predicted concerted k_H/k_D's have been adjusted by 1/0.977.

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