J. Am. Chem. Soc. 1993, 115, 5296–5297

^{14}C KIE in the Diels–Alder Addition of β-Nitrostyrene to 2,3-Dimethylbutadiene. Addition Is Deduced To Be Concerted

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Received March 8, 1993

Whether or not a particular Diels–Alder (DA) reaction is a two-step or concerted process has been debated for years.[1] One experimental approach to answering the question is to relate the configurations of reactants and product. In this approach, for example, Houk and co-workers showed that the prototype addition of ethene to butadiene is concerted.[2] A second experimental approach is to measure kinetic isotope effects for reactants that are labeled at the bonding positions, the premise being that the presence of an isotope effect would signify that bond formation is rate-determining. Deuterium KIEs have been used most frequently in this regard, but interpretation of the results is not without controversy.[3] Labeling the bonding atoms themselves is an attractive alternative, for, in this case, the heavy-atom KIEs are relatable directly to motion of the bonding atoms themselves along the reaction coordinate rather than to concomitant hybridization changes that determine deuterium KIE.

As far as we have been able to find, only one attempt to classify a DA addition with heavy-atom KIE has been reported. This attempt (which appears, in fact, to be one of the earliest attempts to use heavy-atom KIE in solving reaction mechanisms) involved the addition of [2-^{14}C]-1-nitro-2-phenylethene ([2-^{14}C]**1**) (that is, β-nitrostyrene labeled at its α-position) to 2,3-dimethylbutadiene (**2**).[4,5] It was found, in fact, that labeling with ^{14}C at C-2 did not result in a KIE. That result suggests that two-step addition of **1** to **2** occurs, with addition to C-1 of **1** being rate-determining. However, a KIE for labeling at C-1 was not measured.[4]

We have reinvestigated this DA reaction by labeling with ^{14}C, successively, at C-1 and C-2. Substantial and approximately equal KIEs were found for both labelings (Table I). We feel that it is unlikely that these KIEs would result from alternating, competitive, rate-limiting bonding at both C atoms of **1**, a possibility that has been raised with deuterium KIE in a retro-DA reaction,[3a,8] and conclude, therefore, that this DA reaction is concerted.[9]

Table I. KIEs for the Addition of [1-^{14}C]**1** and [2-^{14}C]**1** to **2**

run no.	convn	KIE
	[1-^{14}C]**1**	
1	0.19	1.0448 ± 0.0013
2	0.22	1.0421 ± 0.0035
3	0.27	1.0441 ± 0.0026
4	0.30	1.0444 ± 0.0016
	mean	1.0438 ± 0.0012
	[2-^{14}C]**1**	
5	0.20	1.0491 ± 0.0018
6	0.23	1.0449 ± 0.0009
7	0.30	1.0478 ± 0.0039
8	0.31	1.0479 ± 0.0015
	mean	1.0474 ± 0.0015

We have deduced that the earlier report of no KIE at C-1 erred because the earlier workers assumed in part of their experimental work but did not confirm that 100% conversion had occurred. Sampling for 100% conversion was made by heating a solution of the reactants at reflux overnight.[4] We found that that procedure resulted not only in loss of **2**, but also in a conversion of 61%. Complete conversion was achieved only by heating a solution containing an excess of **2** in a sealed ampule at 115 °C for 3 days. Based on our KIE of 1.0438, the earlier workers' counting data are consistent with 60% rather than the assumed 100% conversion. Ropp and co-workers demonstrated that the cycloaddition was not reversible when **3** was heated as a melt for 24 h at 130 °C.

Experimental Section. [2-^{14}C]-1-nitro-2-phenylethene ([2-^{14}C]**1**) was prepared by reaction of [7-^{14}C]benzaldehyde with nitromethane.[10] [7-^{14}C]benzaldehyde was prepared by reducing commercially-available [7-^{14}C]benzoic acid to [7-^{14}C]benzyl alcohol with $LiAlH_4$ and by next oxidizing the benzyl alcohol with pyridinium chlorochromate.[11] The [^{14}C]nitromethane needed for preparing [1-^{14}C]**1** was made by reaction of [^{14}C]methyl iodide (ChemSyn Science Labs) with silver nitrite.[12] Labeled β-nitrostyrene was purified by chromatography on a silical gel column (hexane/ether, 2:1), followed by crystallization from ethanol, mp 56–58 °C, activity 8.5 mCi/mol.

Diels–Alder Reaction. Low Conversion. The procedures that follow were optimized with reactions of unlabeled **1**. Examples with [2-^{14}C]**1** are given. A solution of 100 mg (1.20 mmol) of **2** and 750 mg (5.00 mmol) of [2-^{14}C]**1** in 3 mL of dry toluene was sealed in a snap-neck ampule. The ampule was placed in a thermostatically-controlled oven at 115 °C for 3 days, after which it was removed, cooled, and opened. The solution was washed into a round-bottom flask, and the solvent and unused **2** were removed on a rotary evaporator. The residue consisted of unused **1** and the product, 1,2-dimethyl-5-nitro-4-phenylcyclohexene (**3**). ^{1}H NMR assay of **1** (doublet for $=CHNO_2$ at 7.77 ppm) and **2** (multiplet for $CHNO_2$ at 4.89–4.76 ppm) showed 20% conversion of **1**. The residue (840 mg) was chromatographed on a silica gel column (230–400 mesh) with cyclohexane/petroleum ether/ether (10:10:1). Collection of 20-mL fractions resulted in clean separation of **1** and **3**, giving 232 mg (1.00 mmol, 20%) of **3** and 581 mg (3.90 mmol) of **1**. **3** was crystallized from cyclohexane and sublimed, giving 179 mg (0.77 mmol, 77%), mp 94–95 °C (lit. mp 91–92 °C[4] and 96 °C[13]). The product was used for scintillation counting.

High Conversion. A solution of 275 mg (3.35 mmol) of **2** and 250 mg (1.68 mmol) of [2-^{14}C]**1** in 3 mL of toluene was treated similarly. ^{1}H NMR assay showed complete conversion of **1**. The crude product (381 mg, 1.65 mmol, 98%) was not chromatographed (no **1** present) but was crystallized from cyclohexane, sublimed, recrystallized, and resublimed to give 219 mg (0.95 mmol, 60%) of **3**, mp 94–96 °C.

KIE Measurements. A sample of 7–8 mg (±0.002 mg) of **3** was weighed on a Cahn balance and dissolved in 10 mL of

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scintillation cocktail (Fisher Biotech ScintiLene BD, No. BP 455-4). Four samples (replicates) from each run (low and 100%) were weighed. Each sample was counted 30 times (3 cycles of 10 counts each), with 2σ set at 0.5%. One low and one high conversion were made for each run, and four runs were made for each label (1-^{14}C and 2-^{14}C). KIEs were calculated in a standard way and are listed in Table I.

Acknowledgment. We thank the National Science Foundation for support under Grant No. CHE-8919768.