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Thermal Rearrangement of Allyl Vinyl Ether: Heavy-Atom Kinetic Isotope Effects and the Transition Structure

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Abstract: Kinetic isotope effects (KIE) in the rearrangement of allyl vinyl ether (**1**, 3-oxa-1,5-hexadiene) to 4-pentenal (**2**) were measured for labeling with ^{14}C at the 2-, 4-, and 6-positions and with ^{18}O at the 3-position. BEBOVIB modeling calculations were applied successfully to the heavy-atom KIE and previously reported KIE for deuterium substitution at positions 4 and 6. From the calculations, it is deduced that the C_4–O bond is 50–70% broken and the C_1–C_6 bond 10–30% formed in the transition structure. Further, there is strong coupling between the allyl and vinyloxy fragments, strong bonding within the allyl but relatively weak bonding within the vinyloxy fragment.

Introduction

The thermal, aliphatic Claisen rearrangement has evoked considerable interest in its applications to synthetic and theoretical organic chemistry.[3] The prototype rearrangement of allyl vinyl ether (**1**) to 4-pentenal (**2**), particularly, has been the focus of theoretical and experimental works that have sought to characterize its transition structure. The rearrangement is formally a [3,3]-sigmatropic shift. The theoretical interest in it has been centered on the nature of the transition state and on whether rearrangement is concerted or is a two-step one in which a 1,4-diradical intermediate participates. Coates and co-workers[4] measured the rates of rearrangement of **1** and 4-, 5-, and 6-methoxy-**1** in several solvents and concluded from the effects of solvent and substituents that the rearrangement of **1** is concerted and has a pronounced dipolar character. Insofar as concertedness is concerned, there was, initially, some controversy over the timing of the bond processes. Based on measurement of deuterium kinetic isotope effects (KIE) in rearrangements of [4-$^2H_2$]-**1** and [6-$^2H_2$]-**1**, Gajewski and Conrad concluded that bond breaking was advanced over bond formation.[5] This conclusion was supported with ab initio calculations by Houk and collaborators[6] but contradicted by earlier MNDO calculations of Dewar and Healy.[7] Later, however, Dewar and Jie,[8] with the use of AM1 calculations, concluded that the rearrangement does seem to follow the course suggested by Gajewski and Conrad.

Recently, we reported carbon and oxygen KIE for the aromatic Claisen rearrangement of allyl phenyl ether.[9,10] Bond-order calculations were made to fit not only these six heavy-atom KIE but also the earlier deuterium KIE of McMichael and Korver.[11] We were able to show that coupled motion within the six-atom pericyclic array led to KIE at the phenyl's C_1 and the allyl's β-carbon atom, that bond breaking (50–60%) was advanced over bond forming (10–20%), and that transition-state coupling was stronger between the three-atom fragments rather than within them.

Scheme I[a]

$$H^{14}COONa \xrightarrow{a} H^{14}COOH \xrightarrow{b} H^{14}COOC_8H_{17} \xrightarrow{c} C_8H_{17}O^{14}CH{=}CH_2$$

[a] Reagents: (a) 85% H_3PO_4 and then drying with B_2O_3; (b) $C_8H_{17}OH$, TsOH; (c) Cp_2TiMe_2.

We have now applied this methodology to the rearrangement of **1** (eq 1). We have measured KIE for rearrangement of [2-^{14}C]-, [4-^{14}C]-, [6-^{14}C]-, and [^{18}O]-**1** and have made cut-off model calculations to attempt to fit these and Gajewski's deuterium[5] KIE to a model of the transition structure.

(1) (2)

(1)

Experimental Section

Preparation of Allyl Vinyl Ether (1). *n*-Octyl vinyl ether was prepared from commercial ethyl vinyl ether and *n*-octanol using the procedure of Watanabe and Conlon[12] and then used as the vehicle for preparing **1**, as follows. A mixture containing 12.9 g (82.6 mmol) of *n*-octyl vinyl ether, 4.0 g (68.9 mmol) of allyl alcohol, and 0.5 g of mercuric acetate was heated so that **1** distilled slowly through a 20-cm Vigreaux column and gave 4.2 g of crude **1**, bp 58–70 °C. The distillate was washed with water three times to remove allyl alcohol and dried over K_2CO_3. Bulb-to-bulb distillation under vacuum gave **1** which was redistilled under normal pressure to give 3.1 g (36.8 mmol, 54%) of **1**, bp 64 °C. The product had satisfactory ^1H NMR and ^{13}C NMR spectra.

Preparations of [4-^{14}C]-**1**, [6-^{14}C]-**1**, and [^{18}O]-**1** were carried out, as described above, in reactions of *n*-octyl vinyl ether with [1-^{14}C]-, [3-^{14}C]-, and [1-^{18}O]allyl alcohol, whose syntheses, themselves, have been reported earlier.[13] [2-^{14}C]-**1** was prepared similarly from reaction of allyl alcohol with *n*-octyl [2-^{14}C]vinyl ether.

***n*-Octyl [2-^{14}C]Vinyl Ether.** This compound was prepared as shown in Scheme I. A mixture of 30 mg of sodium [^{14}C]formate (American

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Radiolabeled Chemicals Inc., 50 mCi/mmol) and 2.69 g of sodium formate (40.0 mmol) in 5.5 mL of 85% phosphoric acid was stirred overnight and then distilled bulb-to-bulb under vacuum to give 3.5 g of a mixture of [^{14}C]formic acid and water. Part of the water was removed from this mixture by stirring overnight with 8.3 g of boric anhydride. Bulb-to-bulb vacuum distillation gave 2.21 g of product representing 1.84 g of formic acid, having a calculated activity of 50 mCi/mol, and 0.37 g of water.

This product was esterified by refluxing with 10 mL (64 mmol) of *n*-octyl alcohol and 5 mg of *p*-toluenesulfonic acid in 150 mL of benzene while a Dean–Stark trap was used to collect water. After reaction was complete (24 h), the benzene was evaporated and the product was purified by column chromatography on silica gel (J. T. Baker, 230–400 mesh) with diethyl ether/petroleum ether 1:1 mixture as eluant. Distillation under normal pressure gave 3.89 g (24.6 mmol, 61%) of *n*-octyl [^{14}C]formate, bp 158 °C. After distillation, 1.0 g of unlabeled *n*-octyl formate was placed in the distillation apparatus and distilled into the labeled product, giving 4.76 g (30.1 mmol) of *n*-octyl [^{14}C]formate, having a calculated activity of 41 mCi/mol.

The labeled *n*-octyl formate was converted into *n*-octyl [2-^{14}C]vinyl ether with the method described by Petasis and Bzowej[14] for the methylenation of dodecyl acetate. To a solution of 7.2 g (34.6 mmol) of dimethyltitanocene[15] in 150 mL of anhydrous tetrahydrofuran was added 2.36 g (14.9 mmol) of *n*-octyl [^{14}C]formate, and the mixture was refluxed for 22 h while protected from light. The THF was concentrated by evaporation, and petroleum ether was added to precipitate a yellow solid. The solid was removed, and the filtrate was evaporated under reduced pressure. The residue was immediately purified by passing through a Florisil column with hexane as eluant to give 1.16 g (7.4 mmol, 50%) of *n*-octyl [2-^{14}C]vinyl ether. Unlabeled *n*-octyl vinyl ether (4.60 g) was added to the labeled compound, and the mixture was distilled under reduced pressure to give 5.47 g (35.0 mmol) of *n*-octyl [2-^{14}C]vinyl ether, bp 115–116 °C, having a calculated activity of 8 mCi/mol.

Thermal Rearrangement of Labeled 1. A standard procedure was used to carry out rearrangements. The treatment of the product depended on the isotopic label and the method of isotope assay. In the case of ^{14}C labeling, product 4-pentenal (**2**) was converted into its dimedone derivative. In the case of ^{18}O labeling, the product was reduced to 4-pentenol which was then converted to its 1-naphthylurethane. Examples of procedures follow.

Rearrangement of [4-^{14}C]-1. (A) Low Conversion. A sample of 362 mg (4.30 mmol) of [4-^{14}C]-**1** was sealed under argon in a snap-neck ampule, which, before use, had been soaked overnight in KOH/ethanol mixture, washed with distilled water, and dried at 160 °C. The sealed ampule was placed in a thermostatically controlled oven at 160 °C. The ampule was removed after 60 min, cooled quickly, and opened. A 20-μL sample of the reaction mixture was used for ^{1}H NMR spectroscopy from which the extent of rearrangement was calculated to be 30%. Assay of **1** was made by using the multiplet (dd) for $CH_2{=}CHO$—allyl at 6.4 ppm and of **2** by using the triplet for —CHO at 9.8 ppm. All of the reaction mixture was next dissolved in 25 mL of ethanol and transferred into a round-bottomed flask which contained 470 mg (3.35 mmol) of dimedone, 2 drops of piperidine, and 1 mL of water. The flask was connected to a distilling head and heated. Unused **1** and 2–3 mL of ethanol distilled off. The solution remaining in the flask was cooled to room temperature, and 10 mL of water was added to precipitate a white solid which was filtered off. After the solid was air dried, 325 mg (9.94 mmol, 73% based on 30% conversion) of the dimedone derivative of 4-pentenal was obtained. The product was purified with column chromatography on silica gel (J. T. Baker, 230–400 mesh) with a diethyl ether/hexane 1:1 mixture as eluant. Finally, the product was sublimed twice, yielding 245 mg (0.71 mmol), mp 97–99 °C (lit.[16] mp 98 °C), for scintillation counting.

(B) 100% Conversion. A sample of 149 mg (1.77 mmol) of [4-^{14}C]-**1** was sealed under argon and heated at 160 °C for 24 h. ^{1}H NMR spectroscopy showed that conversion into 4-pentenal was complete. The product was dissolved in 20 mL of ethanol, and 640 mg (4.56 mmol) of dimedone, two drops of piperidine, and 1 mL of water were added. The mixture was refluxed for 10 min. Workup, as described above, gave 405 mg (1.17 mmol) of dimedone derivative, mp 98 °C. In all, six low-conversion rearrangements of [4-^{14}C]-**1** were carried out in three sets of two ampules. For each set of two low-conversion ampules, one high-conversion ampule was used. The data for all runs are listed in Table I.

Table I. Kinetic Isotope Effects (KIE) for the Thermal Rearrangement of Allyl Vinyl Ether (**1**) to 4-Pentenal (**2**) at 160 °C

run	isotope	conv	KIE
1	^{18}O	0.19	1.0503 ± 0.0012
2		0.19	1.0507 ± 0.0011
3		0.20	1.0501 ± 0.0020
4		0.23	1.0530 ± 0.0011
5		0.25	1.0483 ± 0.0025
6		0.27	1.0515 ± 0.0021
7	2-^{14}C	0.17	1.0264 ± 0.0023
8		0.20	1.0240 ± 0.0010
9		0.24	1.0289 ± 0.0009
10		0.24	1.0291 ± 0.0014
11		0.27	1.0255 ± 0.0018
12		0.30	1.0286 ± 0.0006
13	4-^{14}C	0.14	1.0674 ± 0.0011
14		0.18	1.0704 ± 0.0038
15		0.23	1.0758 ± 0.0008
16		0.24	1.0780 ± 0.0008
17		0.27	1.0776 ± 0.0012
18		0.30	1.0627 ± 0.0016
19	6-^{14}C	0.16	1.0196 ± 0.0004
20		0.20	1.0165 ± 0.0014
21		0.21	1.0156 ± 0.0008
22		0.26	1.0184 ± 0.0023
23		0.30	1.0191 ± 0.0014
24		0.37	1.0176 ± 0.0005

Rearrangement of [^{18}O]-1. (A) Low Conversion. Rearrangement was carried out as described for [4-^{14}C]-**1** with 535 mg (6.36 mmol) of allyl vinyl [^{18}O]ether (12.9% enriched in ^{18}O) for 55 min at 160 °C. For the obvious reason, the dimedone method could not be used. The mixture containing 20% of [^{18}O]-**2** and 80% of [^{18}O]-**1** was dissolved in 15 mL of anhydrous ether and treated with 100 mg of lithium aluminum hydride at 0 °C for 4 h. After reduction of **2** was complete (checked by TLC), 10 mL of 1 N sodium hydroxide was added and the ether layer which contained 4-[^{18}O]pentenol and unreacted [^{18}O]-**1** was separated. Separate experiments with unlabeled **1** showed that **1** was stable under these conditions. The aqueous layer was extracted twice with diethyl ether. The combined ether extracts was dried over K_2CO_3 overnight. Ether and most of [^{18}O]-**1** were evaporated under reduced pressure to leave 4-[^{18}O]pentenol. To this was added 215 mg (1.27 mmol) of 1-naphthyl isocyanate, and the mixture was heated for 5 min. The 1-naphthylurethane of 4-[^{18}O]pentenol which precipitated was purified by column chromatography on silica gel (J. T. Baker, 60-200 mesh) with a diethyl ether/hexane 1:1 mixture as eluant. The product was then crystallized from petroleum ether and sublimed twice to give 234 mg (0.92 mmol, 72% based on 20% conversion), mp 55–58 °C, for mass spectrometry.

(B) 100% Conversion. A sample of 1612 mg (1.91 mmol) of [^{18}O]-**1** was sealed under argon and heated at 160 °C for 24 h to give 4-[^{18}O]pentenal. Reduction with 140 mg of lithium aluminum hydride gave 4-[^{18}O]pentenol, which was converted to its 1-naphthylurethane and purified as described above.

KIE Measurements. Isotope abundances for calculating oxygen KIE were obtained from whole molecule–ion mass ratios measured on the 1-naphthylurethane of 4-[^{18}O]pentenol. A Hewlett-Packard quadrupole mass spectrometer, Model 5995, was used in the SIM mode. Samples were introduced via the solid sample inlet with a direct insertion probe. Relative abundances of the ions having m/z 255 and 257 were measured. Approximately 2000 scans were made per sample and analyzed in 25 blocks of 80 scans each.

Carbon KIE were obtained from ^{14}C abundances measured with scintillation counting in a Beckman Instruments counter, Model LS 5000 TD. A sample (about 9 mg) of the dimedone derivative of labeled 4-pentenal was weighed precisely (±0.002 mg) on a Cahn balance and dissolved in 10 mL of cocktail (Fisher Biotech ScintiLene BD, No. BP 455-4). Four samples (replicates) for each run were weighed. Thus, each measurement was an average of four samples. Each sample was counted 30 times (3 times per 1 cycle, 10 cycles). The 2σ was set at 0.5%.

Details of the methods and of calculating KIE have been described earlier.[17] All KIE are listed in Table I, and the averaged KIE are given in Table II.

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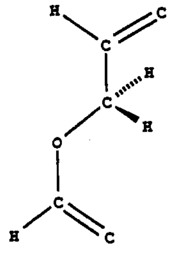
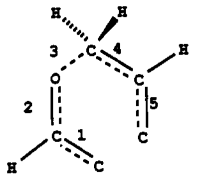
Table II. Averaged KIE for the Rearrangement of **1**

isotope	KIE
^{18}O	1.0506 ± 0.0007
2-^{14}C	1.0271 ± 0.0006
4-^{14}C	1.0720 ± 0.0008
6-^{14}C	1.0178 ± 0.0005

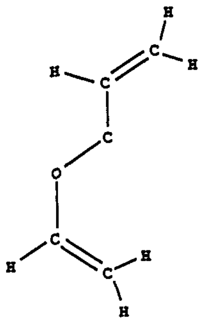
Chart I



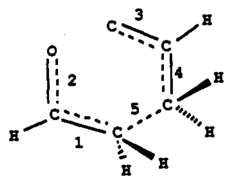
3R



3TS



4R



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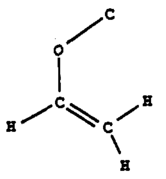
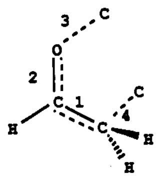


5R



5TS

BEBOVIB Calculations. The model calculations using the BEBOVIB-IV program in a version compiled to run on a Macintosh II computer[18] were carried out as before.[9,10] Models **3R** → **3TS**, **4R** → **4TS**, and **5R** → **5TS** closely resembled those used for the aromatic Claisen rearrangement (Chart I). They follow the cutoff procedures (removal of atoms more than two bonds removed from the site of isotopic substitution) reported by Wolfsberg and Stern[19,20] to give results close to those from full models. As before, we used different models for different patterns of isotopic substitution so as to avoid cyclic structures, which have been shown to introduce redundant coordinates that increase the difficulty of the calculations and complicate the interpretation of the results.[21]

Again, off-diagonal F matrix elements were introduced for the transition structures so as to ensure imaginary reaction coordinate frequencies in which bonding changes were occurring in the appropriate phases to transform the transition structures to products.[22] The off-diagonal elements were calculated from eq 2. The relationships between a_{mn} values for models **3** and **4** are given by eq 3 and for model **5** by eq 4. The a_{mn} values were varied so as to give the best fit to the experimental isotope effects for a given model, subject to two constraints. One was that **3TS**, **4TS**, and **5TS** should have reaction coordinate frequencies of similar absolute magnitudes, and the other was that couplings involving the same pairs of bonds in different models should be similar (they cannot be exactly the same between **3** and **4** on the one hand and **5** on the other because eqs 3 and 4 are different).

$$F_{mn} = a_{mn}(F_{mm}F_{nn})^{1/2} \tag{2}$$

$$1 - a_{12}^2 - a_{23}^2 - a_{34}^2 - a_{45}^2 + a_{12}^2a_{34}^2 + a_{12}^2a_{45}^2 + a_{23}^2a_{45}^2 = D \tag{3}$$

$$1 - a_{12}^2 - a_{23}^2 - a_{34}^2 + a_{12}^2a_{34}^2 = D \tag{4}$$

We used the same criterion for goodness of fit as before,[10] namely, the quantity dev calculated from eq 5. This gives a quantity which behaves

$$\text{dev} = \left(\sum_{1}^{n} ((\text{exptl} - \text{calcd})/\text{exptl})^2/(n-1)\right)^{1/2} \tag{5}$$

in the same way as a standard deviation, though its significance is, of course, different. Large deviations contribute disporportionately because of the squaring of the difference, which avoids a deceptively small value of dev in a case where the difference for one isotopic species is large but small for all of the others. The heavy-atom and H/D effects were treated separately because the relative uncertainties in the latter are much larger than in the former.

In order to give a sense of what the numbers in the dev columns of Tables III and IV mean, the following artificial examples are provided. If all of the heavy-atom isotope effects were in error by a uniform ±0.004, dev would be 0.0044, while an error of ±0.003 would give dev = 0.0033. An error of ±0.02 in the secondary deuterium isotope effects would give dev = 0.0270, while an error of ±0.03 would give dev = 0.0415.

Results and Discussion

Experimental KIE. Substantial KIE were found for breaking the C–O bond (3-^{18}O and 4-^{14}C) and for forming the C–C bond (6-^{14}C). The results remove all question about the mechanism of this rearrangement. It is concerted; a two-step process in which one bond is made (or broken) before the other is broken (or formed) is ruled out. The large 3-^{18}O and 4-^{14}C effects (1.0506 and 1.0720) and the smaller 6-^{14}C (1.0178) effect suggest qualitatively that cleavage of the carbon–oxygen bond contributes more strongly than the formation of the new carbon–carbon bond to the reaction coordinate motion. The experimental isotope effect for the 2-C position (1.0271) demonstrates that, as with the aromatic Claisen case, experimental data can characterize the motion of atoms in a pericyclic array that are not themselves directly involved in bond breaking or forming. Thus, our data collectively show that the six skeletal atoms of this rearrangement are coupled in motion.

BEBOVIB Calculations. Our initial attempts were with five different sets of n(CO) and n(CC) values (the C–O bond is breaking and the C–C bond forming in the transition structure) corresponding to those which gave the best fits for the aromatic Claisen rearrangement.[10] The results in Table III are for a model that is closely similar in bonding to the best model for the aromatic Claisen rearrangement and uses the same sets of a_{mn} values.

There are obvious and serious discrepancies between calculated and experimental values in Table III. The calculated ^{18}O and 4-^{14}C effects are much smaller and the calculated 4,4-D_2 and 6-^{14}C effects are much larger than the experimental values. After considerable trial and error, it became apparent that it was necessary to loosen the carbon–oxygen bond in the developing carbonyl group and tighten the bonding within the allyl group relative to the aromatic Claisen model. Adjustment of the a_{mn} values was also required, in the direction of further increasing the strength of coupling between the two fragments (allyl and vinyloxy) in the transition structures, particularly at the O_3–C_4 end.

An especially troublesome problem was fitting the secondary deuterium isotope effects reported by Gajewski and Conrad.[5] Initially, models that gave good fits to the heavy-atom isotope

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Table III. Calculated Isotope Effects at 160 °C for Model Resembling Aromatic Claisen[a]

n(CO)/n(CC)	^{18}O	4-D_2	4-^{14}C	6-^{14}C	6-D_2	2-^{14}C	dev(hvy)	dev(H/D)
0.5/0.2	1.0350	1.1618	1.0354	1.0338	0.9339	1.0200	0.0243	0.0751
0.5/0.1	1.0350	1.1618	1.0354	1.0360	0.9574	1.0178	0.0250	0.0631
0.4/0.3	1.0334	1.1947	1.0373	1.0353	0.9360	1.0217	0.0239	0.0960
0.3/0.3	1.0318	1.2292	1.0391	1.0401	0.9629	1.0214	0.0247	0.1124
0.4/0.2	1.0334	1.1947	1.0373	1.0386	0.9602	1.0198	0.0248	0.0875
exptl	1.0506	1.092	1.0720	1.0178	0.976	1.0271		

[a] a_{mn} values 0.4, 0.72, 0.57, and 0.4 for model **3**; 0.4, 0.57, and 0.73 for model **4**; and 0.4, 0.72, and 0.83 for model **5**. The order is that of the numbered bonds in the corresponding structures starting with C_1 and proceeding clockwise, skipping over bonds that are cut off in the models. Tunnel corrections calculated from the first term of the Bell equation are included in all isotope effects but change the effects by less than experimental error.

Table IV. Calculated Isotope Effects at 160 °C for Best Model[a]

n(CO)/n(CC)	^{18}O	4-D_2	4-^{14}C	6-^{14}C	6-D_2	2-^{14}C	dev(hvy)	dev(H/D)
0.9/0.1	1.0399	1.0049	1.0489	1.0268	1.0791	1.0117	0.0173	0.1290
0.7/0.3	1.0398	1.0645	1.0537	1.0190	0.9704	1.0135	0.0140	0.0265
0.5/0.5	1.0391	1.1315	1.0580	1.0155	0.9317	1.0155	0.0120	0.0590
0.3/0.7	1.0372	1.2082	1.0607	1.0123	0.8973	1.0181	0.0114	0.1302
0.1/0.9	1.0322	1.2730	1.0575	1.0096	0.8668	1.0220	0.0141	0.1900
0.7/0.2	1.0475	1.0643	1.0581	1.0206	0.9912	1.0274	0.0079	0.0302
0.7/0.1	1.0468	1.0650	1.0613	1.0225	1.0136	1.0254	0.0068	0.0449
0.6/0.3	1.0474	1.0779	1.0588	1.0186	0.9699	1.0286	0.0075	0.0145
0.6/0.2	1.0468	1.0785	1.0620	1.0202	0.9907	1.0267	0.0060	0.0194
0.6/0.1	1.0461	1.0792	1.0653	1.0222	1.0133	1.0246	0.0052	0.0387
0.5/0.4	1.0470	1.1116	1.0609	1.0167	0.9500	1.0294	0.0065	0.0326
0.5/0.3	1.0465	1.1122	1.0642	1.0181	0.9693	1.0277	0.0048	0.0194
0.5/0.2	1.0459	1.1128	1.0674	1.0197	0.9902	1.0261	0.0038	0.0236
0.5/0.1	1.0452	1.0945	1.0691	1.0218	1.0129	1.0240	0.0044	0.0365
0.4/0.3	1.0453	1.1099	1.0659	1.0175	0.9687	1.0277	0.0044	0.0178
0.4/0.2	1.0448	1.1105	1.0693	1.0192	0.9896	1.0258	0.0037	0.0216
0.4/0.1	1.0442	1.1110	1.0727	1.0215	1.0125	1.0237	0.0046	0.0399
0.3/0.3	1.0439	1.1278	1.0689	1.0169	0.9680	1.0277	0.0041	0.0328
0.3/0.2	1.0434	1.1283	1.0723	1.0187	0.9890	1.0257	0.0041	0.0348
0.3/0.1	1.0429	1.1287	1.0759	1.0211	1.0120	1.0237	0.0055	0.0482
0.99/0.01[b]	1.0004	1.0090	0.9999	1.0015	1.0046	0.9989		
0.01/0.99[b]	1.0103	1.2874	1.0228	0.9807	0.7244	1.0009		
exptl	1.0506	1.092	1.0720	1.0178	0.976	1.0271		

[a] a_{mn} values 0.25, 0.7, 1.0, and 0.25 for model **3**; 0.25, 0.25, 0.2, and 1.0 for model **4**; and 0.25, 0.7, and 1.1 for model **5**. The order is that of the numbered bonds in the corresponding structures starting with C_1 and proceeding clockwise, skipping over bonds that are cut off in the models. Tunnel corrections calculated from the first term of the Bell equation are included in all isotope effects but change the effects by less than experimental error. [b] Isotope effects for very reactantlike and productlike species, respectively, in order to check that the force field leads to no isotope effect in the former and an equilibrium isotope effect in the latter case. All $a_{mn} = 0$.

effects gave poor fits to the secondary deuterium isotope effects, particularly at the 6-position. The basic difficultly in modeling the 6,6-D_2 effect is that formation of a new C_6–C_1 bond introduces new bending coordinates involving the 6-hydrogens. Other things being equal, this tends to depress the 6,6-D_2 isotope effect below the value expected from rehybridization alone. This problem was dealt with by following a suggestion from Professor W. P. Huskey. The Huskey procedure involves using redundant sets of coordinates such that all bending coordinates of *both* the reactant and the product are represented in the transition structure. Thus, the C–H bonds at the C_4- and C_6-positions are given out-of-plane bending coordinates in the transition structure (even though these carbon atoms and the attached hydrogens do not lie in a plane) whose force constants vary with n(CO) and n(CC), disappearing at the reactant extreme in the former case and at the product extreme in the latter.

That this procedure is physically reasonable is shown by the models in the third and second from the last lines in Table IV, which represent very reactantlike and productlike species, respectively. The former should give isotope effects near unity, which they do, and the latter should give values close to the equilibrium isotope effects. The 4,4-D_2 effect (1.2874) is, in fact, close to the experimental estimate (1.27) of Gajewski and Conrad.[5] The 6,6-D_2 effect (0.7244), however, is substantially below their estimate of 0.86. Nonetheless, our model is capable of matching the experimental *kinetic* isotope effects rather well. The only ways in which the agreement with the 6,6-D_2 equilibrium isotope effect could be improved would be by using different algorithms to relate bond orders and force constants at the 4- and 6-positions or by reducing the C–C–H bending force constants at the 6-position to a value well below that which has given realistic results in previous contexts. No justification for either of these procedures is apparent, and they would certainly affect the fits to the kinetic isotope effects as well.

The final results are shown in Table IV, which includes a large set of n(CO)/n(CC) values so as to make sure that all plausible combinations of bond orders, other than those in Table III, were tried. The first five entries in Table IV are for completely synchronous models (the sum of n(CO) and n(CC) always equal to 1.0). They all give poor fits to the heavy-atom isotope effects, though one case, n(CO) = 0.3, fits the secondary deuterium isotope effects satisfactorily. The heavy-atom effects permit the exclusion of this and a number of other models which fit the deuterium isotope effects alone. The best models for all isotope effects are the ones with extents of bond breaking and bond making very similar to those for the aromatic Claisen rearrangement: n(CO)/n(CC) of 0.5/0.2 and 0.4/0.2 for the aliphatic compared to 0.5/0.1 and 0.4/0.2 for the aromatic Claisen. Almost as good are the fits for 0.3/0.3 and 0.3/0.2. Poorer, but still not unreasonable, are the fits for 0.5/0.1 and 0.4/0.3. We can thus conclude that n(CO) lies in the range 0.3–0.5, while n(CC) lies in the range 0.1–0.3. The comparison of experiment and calculation thus indicates a transition structure which is reactantlike with respect to bond formation (10–30%) but central to productlike with respect to bond cleavage (50–70%).

The calculated equilibrium heavy-atom isotope effects (second from last line, Table IV) are all rather small, as expected from the fact that the total bond order to each of these atoms is the same in the product as in the reactant. Only the nature of the bonding changes, and there is, of course, no contribution due to reaction–coordinate motion. The irreversibility of the rearrangement precludes the direct experimental measurement of these effects. Indeed, the experimental equilibrium isotope effects[5] are estimates on the basis of results in related systems.

Our model agrees very well with the conclusion of Gajewski and Conrad[5] with respect to bond formation ($^1/_6$, or 17%) but less well for bond cleavage ($^1/_3$, or 33%). It is evident, however, that all of our models with n(CO) in the range deduced by Gajewski and Conrad (0.6–0.7) fit the observed heavy-atom isotope effects rather poorly. Furthermore, it is difficult, qualitatively, to reconcile the large 3-^{18}O and 4-^{14}C effects with a reactantlike O_3–C_4 bond in the transition structure. The 4,4-D_2 effect alone allows a range of 0.7 to almost 0.3 for n(CO), if an error of ± 0.03 in the experimental value is conceded. For these reasons, we believe that the extent of bond cleavage in the transition structure is 50% or more.

In addition to giving information about bond orders in the transition structure, the heavy-atom isotope effects allow conclusions about the dynamics of the process. It is clear both from the magnitudes of the 3-^{18}O and 4-^{14}C effects relative to that of the 6-^{14}C effect and from the greater couplings required to reproduce the former than the latter that cleavage of the O_3–C_4 bond contributes more to the reaction coordinate motion than formation of the C_6–C_1 bond.

Finally, ab initio quantum mechanical calculations by Vance and co-workers[6] find that in the transition structure, the C–O bond is stretched 37% from the length of that in **1** and that the forming C–C bond differs from the bond in **2** by 47%. As we have pointed out before,[9] their bond distances translate approximately into bond orders of $n(\mathrm{CO}) = 0.18$ and $n(\mathrm{CC}) = 0.09$, even lower than those from our calculations.

In summary, the BEBOVIB calculations arrive at a transition structure similar to but looser with respect to bond cleavage than that defined by Gajewski and Conrad. The heavy-atom KIE give, again, important information about the dynamics of the process.[9,10]

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