

Carbon Kinetic Isotope Effects and Transition Structures in the Rearrangements of Allyl Vinyl Ethers.

2-(Trimethylsiloxy)- and 2-(Methoxycarbonyl)-3-oxa-1,5-hexadiene

Lidia Kupczyk-Subotkowska,[†] William H. Saunders, Jr.,^{*,‡} Henry J. Shine,^{*,†} and Witold Subotkowski[†]

Contribution from the Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, Texas 79409, and Department of Chemistry, University of Rochester, River Station, Rochester, New York 14627

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Abstract: ¹⁴C KIE (kinetic isotope effects) were measured for the C-1, C-2, C-4, and C-6 positions in the rearrangement of 2-(trimethylsiloxy)- (1a) and 2-(methoxycarbonyl)-3-oxa-1,5-hexadiene (1b). The data, along with earlier C-4 and C-6 deuterium KIE, were fitted to Bebovib modeling calculations. The calculations show that in the transition structure (TS) for 1a 70–80% bond breaking and 20% of bond making occurs, whereas in the TS of 1b both bond breaking and bond making amount to 30–40%. Results for 1a and 1b are compared with earlier results for the parent compound, allyl vinyl ether.

The rearrangement of allyl vinyl ethers (aliphatic Claisen rearrangements) and related systems has theoretical, synthetic, and biological importance.^{1,2} Theoretical interest has centered on the question of concertedness and on the natures of transition states. Within recent years, the timing of bond breaking and bond forming in the rearrangement of allyl vinyl ether itself has been described with the aid of theoretical computations^{3,4} and heavy-atom kinetic isotope effects (KIE).⁵ By fitting Bebovib modeling calculations to the oxygen and carbon KIE and to earlier measured deuterium KIE,⁶ we were able to show that in the transition structure (TS) of the rearrangement of allyl vinyl ether into 4-pentenal (eq 1) at 160 °C the C₄—O bond was 50–70% broken and the new C₁—C₆ bond 10–30% formed.⁵



Gajewski has applied the deuterium KIE method of characterizing transition structures to derivatives of allyl vinyl ether,⁷ among which the results for the 2-(trimethylsiloxy) and 2-(methoxycarbonyl) derivatives were particularly interesting to us. Rearrangement of allyl vinyl ether takes place at reasonable rates only at relatively high temperatures,^{8,9} whereas the 2-(trimethylsiloxy) derivative (2-(trimethylsiloxy)-3-oxa-1,5-hexadiene, 1a) rearranges at room temperature.^{10,11} This difference

led Gajewski and Emrani¹² to measure deuterium KIE in the rearrangements of [4,4-²H₂]1a and [6,6-²H₂]1a. From those measurements and computed equilibrium isotope effects (EIE) it was concluded that the TS in rearrangement of 1a was looser than that of allyl vinyl ether, bond-breaking in 1a being much more advanced. Advanced bond-breaking was attributed to the stabilizing effect of the trimethylsiloxy group on the vinyloxy portion of the TS.¹² In contrast, an analogous study of the rearrangement of the 2-(methoxycarbonyl) derivative, 2-(methoxycarbonyl)-3-oxa-1,5-hexadiene (1b), led to the conclusion that bond breaking in its TS was less advanced, and bond making more advanced than in the parent compound.^{2,7} We were attracted, then, to testing the ability of heavy-atom KIE, combined with Bebovib modeling calculations, to characterize the TS of these arrangements, and set out to measure ¹⁴C KIE in the rearrangements of 1a and 1b. After our work was complete, however, Gajewski and co-workers questioned earlier assumptions in relating deuterium KIE and EIE measurements,¹³ particularly for product-like TS, and deduced that bond breaking in the rearrangement of 1a was significantly less advanced than had been thought earlier.¹² We report here our KIE results for 1a and 1b and the Bebovib modeling calculations that fit not only them but also the published deuterium KIE.^{2,7,12} The data lead to a difference with Gajewski's new view of the TS for 1a, and this is brought out in the discussion.

KIE Results: 1a

Rearrangement of 1a gives 2a, but for workup the 2a was converted into 4-pentenoic acid (6), and for KIE measurements, 6 was converted into its more easily purifiable anilide, Scheme 1. The 1a was labeled with ¹⁴C, successively, in its 1-, 2-, 4-, and 6-positions, using appropriately labeled, commercial, sodium acetate and synthesized allyl alcohols¹⁴ as the sources of ¹⁴C. Trimethylsilylation of labeled allyl acetate was carried out as

[†] Texas Tech University.

[‡] University of Rochester.

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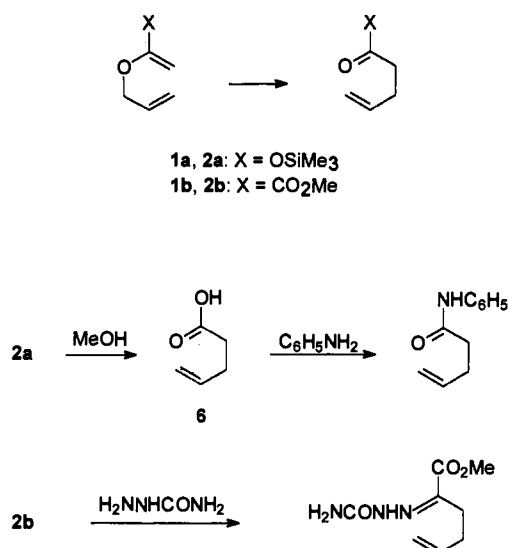
- (1) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423.
- (2) Gajewski, J. J.; Jurayj, J.; Kimbrough, D. R.; Gande, M. E.; Ganem, B.; Carpenter, B. K. *J. Am. Chem. Soc.* **1987**, *109*, 1170.
- (3) Vance, R. L.; Rondon, N. G.; Houk, K. N.; Jensen, H. F.; Borden, W. T.; Komornicki, A.; Wimmer, E. *J. Am. Chem. Soc.* **1984**, *106*, 7127.
- (4) Dewar, M. J. S.; Jie, C. *J. Am. Chem. Soc.* **1989**, *111*, 511.
- (5) Kupczyk-Subotkowska, L.; Saunders, W. H., Jr.; Shine, H. J.; Subotkowski, W. *J. Am. Chem. Soc.* **1993**, *115*, 5957.
- (6) Gajewski, J. J.; Conrad, N. D. *J. Am. Chem. Soc.* **1979**, *101*, 6693.
- (7) Gajewski, J. J. In *Isotopes in Organic Chemistry*; Buncl, E., Lee, C., Eds.; Elsevier: New York, 1987; Vol. 7, Chapter 3.
- (8) Hurd, C. D.; Pollock, M. A. *J. Am. Chem. Soc.* **1938**, *60*, 1905.
- (9) Schuler, F. W.; Murphy, G. W. *J. Am. Chem. Soc.* **1950**, *72*, 3155.
- (10) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897.
- (11) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

(12) Gajewski, J. J.; Emrani, J. *J. Am. Chem. Soc.* **1984**, *106*, 5733.

(13) Gajewski, J. J.; Olson, L. P.; Tupper, K. J. *J. Am. Chem. Soc.* **1993**, *115*, 4548.

(14) Kupczyk-Subotkowska, L.; Shine, H. J. *J. Labelled Compd. Radiopharm.* **1992**, *31*, 381.

Scheme 1

Table 1. Conversions (*F*) and Yields of 4-Pentenoic Acid (**6**) in the Rearrangement of **1a** to **2a**

run	time for low conv, h	<i>F</i> , by NMR	isolated, crude 6		yield (<i>C</i>) ^d of 6 , %
			low conv, mmol ^b	100% conv, mmol ^c	
1	3.0	0.18	2.11	2.09	46
2	4.0	0.28	2.95	3.06	47
3	4.25	0.32	3.78	2.20	47
4	3.0	0.20	2.56	1.91	49
5	3.0	0.18	1.30	3.76	37
6	4.0	0.32	2.97	3.05	41
7 ^a	3.5	0.22	1.30	1.60	25
8 ^a	4.0	0.28	1.12	1.40	18
9 ^a	3.5	0.22	1.30	0.91	25
10	3.5	0.21	2.32	3.50	48
11	4.0	0.32	3.33	3.24	46
12	3.5	0.23	2.33	4.62	49

^a Isolated **1a** was used. ^b *A*, in calculating *C*. ^c *B*, in calculating *C*. ^d 100[(*A*/*F*) + *B*]/(allyl acetate)₀, where (allyl acetate)₀ = 30.0 mmol.

described by Emrani.¹⁵ Initially, **1a** was isolated by distillation, as described by Emrani,^{12,15} but the losses in this procedure were so large that the major part of our work (nine runs out of 12, Table 1) was performed with **1a** *in situ*. Preparation of **1a** and allowing it to rearrange *in situ* was carried out also as described by Emrani,¹⁵ but our KIE measurements were made, therefore, on rearrangements in the *in situ* solvent tetrahydrofuran (THF) rather than the added CCl₄ that Emrani needed for NMR measurements. Trimethylsilylation of an ester enolate can occur at oxygen or carbon.^{16,17} Because of this, conversions of an enolate into a (trimethylsilyl)oxy derivative may be low. Not much appears to have been said directly about C-trimethylsilylation of allyl acetate. Ireland and co-workers reported a yield of 66% of **1a** (after methanolysis to **6**) and that some C-trimethylsilylated-**6** (whose origin was possibly C-(trimethylsilyl)-**2a**¹⁰) was obtained, too.^{10,11}

KIE measurements require that rearrangements be stopped after low conversion and also be allowed to continue to completion. Low conversions of **1a** were measured by ¹H NMR spectroscopy, but yields of product themselves were measured after methanolysis of **2a** to **6**. We were not concerned with optimizing yields, and these, given in Table 1, are lower than Ireland's, reaching only

(15) Emrani, J. Ph.D. Dissertation, Indiana University, 1985; *Diss. Abstr. Int.*, B 1986, 46 (6), 1922; *Chem. Abstr.* 1986, 105, 41981a. We thank Prof. Gajewski for supplying us with relevant portions of the dissertation and for helpful discussion about the isolation of **1a**.

(16) Welch, J. T.; Plummer, J. S.; Chou, T.-S. *J. Org. Chem.* 1991, 56, 353.

(17) Rathke, M. W.; Sullivan, D. F. *Synth. Commun.* 1973, 3, 67.

Table 2. ¹⁴C KIE for the Rearrangement of 2-(Trimethylsilyloxy)-3-oxa-1,5-hexadiene (**1a**) to 1-(Trimethylsilyloxy)-4-pentenal (**2a**) in THF at 22 °C

run ^a	labeled position	conv	KIE ^b
1	1	0.18	1.0160 ± 0.0028
2	1	0.28	1.0144 ± 0.0018
3	1	0.32	1.0188 ± 0.0022
	av		1.0164 ± 0.0013
4	2	0.20	1.0285 ± 0.0036
5	2	0.18	1.0192 ± 0.0037
6	2	0.32	1.0244 ± 0.0036
	av		1.0240 ± 0.0021
7 ^c	4	0.22	1.1122 ± 0.0045
8 ^c	4	0.28	1.0919 ± 0.0031
9 ^c	4	0.22	1.1104 ± 0.0039
	av		1.1048 ± 0.0022
10	6	0.21	1.0199 ± 0.0024
11	6	0.32	1.0151 ± 0.0014
12	6	0.23	1.0171 ± 0.0012
	av		1.0174 ± 0.0010

^a Each run is an average of four measurements. ^b From scintillation counting data on the anilide of **6**. ^c Isolated **1a** was used. In all other cases rearrangement occurred *in situ*.

Table 3. ¹⁴C KIE for the Rearrangement of 2-(Methoxycarbonyl)-3-oxa-1,5-hexadiene (**1b**) to Methyl 2-Oxo-5-hexenoate (**2b**) in CCl₄ at 80 °C

run ^a	labeled position	conv	KIE ^b
1	1	0.25	1.0289 ± 0.0018
2	1	0.26	1.0270 ± 0.0021
3	1	0.28	1.0280 ± 0.0018
	av		1.0280 ± 0.0011
4	2	0.23	1.0081 ± 0.0017
5	2	0.26	1.0089 ± 0.0016
6	2	0.28	1.0091 ± 0.0013
	av		1.0087 ± 0.0009
7	4	0.26	1.0323 ± 0.0019
8	4	0.27	1.0355 ± 0.0018
9	4	0.28	1.0313 ± 0.0013
	av		1.0330 ± 0.0009
10	6	0.25	1.0113 ± 0.0015
11	6	0.26	1.0113 ± 0.0014
12	6	0.29	1.0129 ± 0.0015
	av		1.0118 ± 0.0008

^a Each run is an average of four measurements. ^b From scintillation counting data on the semicarbazone of **2b**.

nearly 50%. The **6** that we isolated contained an impurity which we assume was 2-(trimethylsilyl)-**6** and which was removed with column chromatography. The remaining losses are attributed to C-silylation of allyl acetate, giving a product that could not undergo methanolysis and hence went to waste.

Isotope effects were measured from scintillation counting data on the anilide of **6**. This derivative was chosen because it is colorless and thus does not cause scintillation quenching, and because as a solid it could be purified by crystallization and sublimation. Three separate rearrangements were carried out for each of the labeled **1a**. The results are given in Table 2.

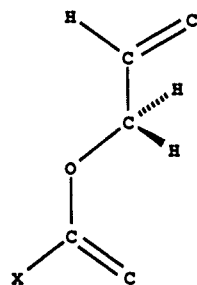
KIE Results: **1b**

Rearrangement of **1b** gives **2b**. For KIE measurements, **2b** was converted into its semicarbazone, Scheme 1, which was more easily purified by sublimation. The **1b** was labeled with ¹⁴C, successively, in its 1-, 2-, 4-, and 6-positions, for which it was necessary to prepare, respectively, [¹⁴C]Eschenmoser's salt,¹⁸ dimethyl [2-¹⁴C]diazomalonnate, and appropriately labeled allyl alcohols.¹⁴ Rearrangements were carried out in CCl₄ at 80 °C. Conversions were monitored by ¹H NMR spectroscopy. Results are listed in Table 3.

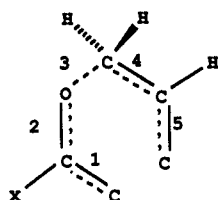
(18) Kupczyk-Subotkowska, L.; Shine, H. J. *J. Labelled Compd. Radiopharm.* 1993, 33, 301.

Bebovib Calculations

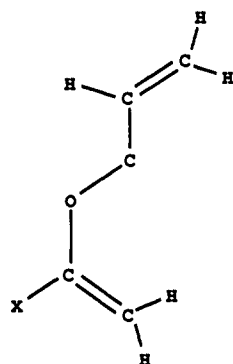
The model calculations using the Bebovib-IV program in a version compiled to run on a Macintosh II computer¹⁹ were carried out as before.^{5,20,21} The models 3R → 3TS, 4R → 4TS, and 5R → 5TS resembled closely those used for the rearrangement of allyl vinyl ether,⁵ except that a substituent X replaces a hydrogen.



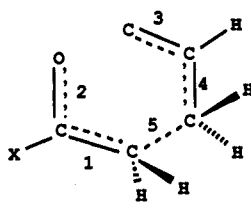
3Ra, X = O
3Rb, X = C



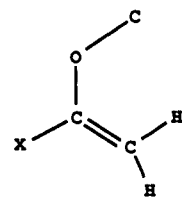
3TSa, X = O
3TSb, X = C



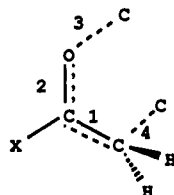
4Ra, X = O
4Rb, X = C



4TSa, X = O
4TSb, X = C



5Ra, X = OSi
5Rb, X = C(=O)O



5TSa, X = OSi
5TSb, X = C(=O)O

They follow the cutoff procedures (removal of atoms more than two bonds removed from the site of isotopic substitution) reported by Wolfsberg and Stern^{22,23} to give results close to those from full models. Only as much of each substituent (OSiMe₃ and CO₂-Me, respectively) as is necessary to satisfy the cutoff procedure is included. 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.²⁴

Again, off-diagonal F matrix elements were introduced for the transition structures so as to ensure imaginary reaction coordinate

(19) Sims, L. B.; Burton, G. W.; Lewis, D. E. Bebovib-IV, QCPE no. 337, Department of Chemistry, Indiana University, Bloomington, IN 47405.

(20) Kupczyk-Subotkowska, L.; Saunders, W. H., Jr.; Shine, H. J. *J. Am. Chem. Soc.* **1988**, *110*, 7153.

(21) Kupczyk-Subotkowska, L.; Subotkowski, W.; Saunders, W. H., Jr.; Shine, H. J. *J. Am. Chem. Soc.* **1992**, *114*, 3441.

(22) Wolfsberg, M.; Stern, M. J. *Pure Appl. Chem.* **1964**, *8*, 225.

(23) Stern, M. J.; Wolfsberg, M. *J. Chem. Phys.* **1966**, *45*, 4105.

(24) Keller, J. H.; Yankwich, P. *J. Am. Chem. Soc.* **1974**, *96*, 2303.

frequencies in which bonding changes were occurring in the appropriate phases to transform the transition structures to products.²⁵ The off-diagonal elements are 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). The Huskey method of dealing with bending coordinates of the allylic hydrogens, previously described by us,⁵ was employed.

We used the same criterion for goodness of fit as before,^{5,21} namely, the quantity Dev calculated from eq 5. This gives a quantity which behaves in the same way as a standard deviation, though its significance is, of course, different. Large deviations contribute disproportionately 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 are treated separately because the relative uncertainties in the latter are much larger than in the former. The calculated KIE for the trimethylsilyloxy derivative are listed in Table 4, and those for the methoxycarbonyl derivative are listed in Table 5. Each includes, out of a range of sets of a_{mn} values, the models which gave the closest agreement with the experimental KIE. The range of $n(\text{CO})$ and $n(\text{CC})$ values in each table is judged sufficient to establish that no other reasonable combinations could give comparable agreement. $n(\text{CO})/n(\text{CC})$ values of 0.99/0.01 for very reactant-like and 0.01/0.99 for very product-like transition structures are included. The former should give KIE close to unity, and the latter should be a measure of equilibrium isotope effects (EIE).

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

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

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

$$\text{Dev} = \left(\sum_1^n ((\text{exptl} - \text{calcd})/\text{exptl})^2 / (n-1) \right)^{1/2} \quad (5)$$

Discussion

The models (3–5, X = H) used to treat isotope effects in the rearrangement of the parent compound, allyl vinyl ether,⁵ were used as starting points in the calculations on the 2-(trimethylsilyloxy) and 2-(methoxycarbonyl) derivatives. The results on the parent compound were in partial agreement with conclusions based on secondary deuterium isotope effects. Our calculations predicted 50–70% bond breaking and 10–30% bond making in the transition structure, while the earlier conclusions from secondary deuterium isotope effects alone predicted about 42% bond breaking and 17% bond making.^{6,7} There is qualitative agreement on a loose transition structure with more bond breaking than bond making, but disagreement on the extent of bond breaking.

The secondary deuterium isotope effects on the 2-(trimethylsilyloxy) derivative predicted a still looser transition structure with about 85% bond breaking and only 29% bond making.^{7,12} Our calculations (Table 4) are in good agreement with these predictions, the best model being the one with both $n(\text{CO})$ and

(25) Melander, L.; Saunders, W. H., Jr. *Reaction Rates of Isotopic Molecules*; Wiley-Interscience: New York, 1980; pp 64–66.

Table 4. Calculated KIE for the 2-(Trimethylsiloxy) Derivative^a

$n(\text{CO})/n(\text{CC})$	1-C-14	2-C-14	4-C-14	6-C-14	4,4-D ₂	6,6-D ₂	Dev(hvy)	Dev(H/D)
0.5/0.3	1.0253	1.0239	1.0751	1.0143	1.3127	0.9070	0.0168	0.1279
0.5/0.2	1.0179	1.0232	1.0817	1.0180	1.3143	0.9435	0.0124	0.1292
0.5/0.1	1.0096	1.0028	1.0882	1.0207	1.3159	0.9837	0.0098	0.1419
0.4/0.4	1.0324	1.0236	1.0776	1.0128	1.3634	0.8714	0.0173	0.1003
0.4/0.3	1.0253	1.0227	1.0842	1.0153	1.3650	0.9070	0.0121	0.0850
0.4/0.2	1.0179	1.0221	1.0908	1.0180	1.3666	0.9435	0.0075	0.0876
0.4/0.1	1.0096	1.0218	1.0974	1.0207	1.3682	0.9837	0.0059	0.1062
0.3/0.4	1.0324	1.0225	1.0862	1.0128	1.4131	0.8739	0.0136	0.0684
0.3/0.3	1.0253	1.0216	1.0929	1.0153	1.4147	0.9070	0.0082	0.0475
0.3/0.2	1.0179	1.0210	1.0996	1.0180	1.4163	0.9435	0.0033	0.0530
0.3/0.1	1.0096	1.0207	1.1063	1.0207	1.4179	0.9837	0.0048	0.0807
0.2/0.4	1.0324	1.0213	1.0943	1.0128	1.4606	0.8739	0.0110	0.0511
0.2/0.3	1.0253	1.0205	1.0892	1.0153	1.3541	0.9070	0.0099	0.0936
0.2/0.2	1.0179	1.0199	1.1080	1.0180	1.4638	0.9435	0.0030	0.0302
0.2/0.1	1.0096	1.0197	1.1149	1.0207	1.4655	0.9837	0.0072	0.0685
0.1/0.4	1.0223	1.0203	1.1018	1.0066	1.5068	0.8071	0.0075	0.1373
0.1/0.3	1.0253	1.0195	1.1088	1.0153	1.5085	0.9070	0.0061	0.0219
0.1/0.2	1.0179	1.0190	1.1158	1.0180	1.5193	0.9435	0.0064	0.0382
0.99/0.01 ^b	0.9903	0.9973	1.0053	1.0024	1.0047	1.0054		
0.01/0.99 ^b	1.0034	1.0000	1.0347	0.9793	1.5006	0.7234		
exptl	1.0164	1.0240	1.1048	1.0174	1.48	0.917		

^a a_{mn} values 0.15, 0.9, 0.25, 1.0 for model 3a; 0.15, 0.9, 0.02, 1.0 for model 4a; 0.3, 1.0, 1.0 for model 5a. The order is that of the numbered bonds in the corresponding structures, starting with C-1 and proceeding clockwise. Temperatures are 22 °C for the heavy-atom and 25 °C for the deuterium effects. 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 reactant-like and product-like 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 $a_{mn} = 0$.

Table 5. Calculated KIE for the 2-(Methoxycarbonyl) Derivative^a

$n(\text{CO})/n(\text{CC})$	1-C-14	2-C-14	4-C-14	6-C-14	4,4-D ₂	6,6-D ₂	Dev(hvy)	Dev(H/D)
0.9/0.1	1.0109	1.0119	1.0272	1.0192	1.0451	0.9910	0.0113	0.1087
0.8/0.2	1.0182	1.0107	1.0284	1.0171	1.0746	0.9581	0.0069	0.0656
0.8/0.1	1.0109	1.0114	1.0339	1.0192	1.0758	0.9910	0.0108	0.0915
0.7/0.3	1.0245	1.0097	1.0309	1.0151	1.1205	0.9279	0.0030	0.0264
0.7/0.2	1.0182	1.0101	1.0354	1.0171	1.1078	0.9581	0.0065	0.0514
0.6/0.4	1.0305	1.0090	1.0318	1.0131	1.1412	0.8999	0.0017	0.0217
0.6/0.3	1.0245	1.0091	1.0373	1.0151	1.1425	0.9279	0.0036	0.0276
0.6/0.2	1.0182	1.0095	1.0430	1.0171	1.1439	0.9581	0.0084	0.0544
0.6/0.1	1.0109	1.0102	1.0259	1.0192	1.1273	0.9910	0.0114	0.0820
0.5/0.5	1.0363	1.0086	1.0340	1.0112	1.1789	0.8741	0.0047	0.0647
0.5/0.4	1.0305	1.0084	1.0394	1.0131	1.1802	0.8999	0.0039	0.0522
0.5/0.3	1.0245	1.0085	1.0449	1.0151	1.1815	0.9279	0.0071	0.0555
0.5/0.2	1.0182	1.0089	1.0502	1.0171	1.1827	0.9581	0.0114	0.0730
0.4/0.5	1.0363	1.0079	1.0418	1.0112	1.2215	0.8741	0.0067	0.0927
0.99/0.01 ^b	0.9921	0.9974	1.0005	1.0019	1.0048	1.0053		
0.01/0.99 ^b	1.0045	0.9970	1.0271	0.9862	1.3992	0.7670		
exptl	1.0280	1.0087	1.0330	1.0118	1.12	0.91		

^a a_{mn} values 0.15, 0.9, 0.05, 1.0 for model 3b; 0.15, 0.9, 0.02, 1.0 for model 4b; 0.15, 1.0, 1.0 for model 5b. The order is that of the numbered bonds in the corresponding structures, starting with C-1 and proceeding clockwise. Temperatures are 80 °C for the heavy-atom and 61.5 °C for the deuterium effects. 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 reactant-like and product-like 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 $a_{mn} = 0$.

$n(\text{CC}) = 0.2$. The only models yielding even passable fits agree that bond breaking exceeds 70% and bond making is no greater than 20%.

A paper by Gajewski, Olson, and Tupper that appeared when our modeling was nearly complete, however, calls into question the basis of this agreement.¹³ In the earlier work,^{7,12} it was assumed that the secondary deuterium isotope effect varied monotonically with the extent of bond breaking at the 4-position and with the extent of bond making at the 6-position. Bebovib calculations assume a similar variation of the stretching and bending force constants associated with the partial bonds in the transition structure, though the result is not necessarily a simple monotonic variation of the isotope effects, particularly those for the heavy atoms. The Gajewski, Olson, and Tupper paper presents persuasive evidence that conversion of the terminal CH₂ of an olefin to the CH₂ of an allyl radical results in loosening of the C—H bending motions such that an isotope effect of 6–10% per D can be expected. To the extent that the migrating allyl group possesses radical character, there can be a contribution to the

secondary deuterium isotope effect in the transition structure that is absent in both the reactant and the product. The maximum isotope effect that can be observed is thus not limited to the equilibrium isotope effect that one would expect for a very product-like transition structure.

Revised algorithms that take this factor into account are then presented for estimating the extents of bond breaking and bond making from the secondary deuterium isotope effects. The conclusions for the parent compound are not greatly altered: 40% bond breaking (42% by the former algorithm) and 10% bond making (17% by the old algorithm). The comparison with our conclusions⁵ (50–70% bond breaking and 10–30% bond making) is essentially unaffected.

The same cannot be said for the 2-(trimethylsiloxy) derivative. The new approach predicts 50–60% bond breaking (85% by the old algorithm) and 40% bond making (29% by the old algorithm). This is in much poorer agreement with our prediction of 70–80% bond breaking and 20% bond making. It is clear from a perusal of Table 4 that no models with as little bond breaking and as

much bond making as demanded by the revised algorithm are acceptable. Possibly we could improve agreement by using different algorithms for the variation of force constants with bond orders. The deuterium isotope effects for allyl radical formation¹³ might serve as guidelines for the construction of such algorithms, but there is no comparable evidence of the effect radical character might have on the heavy-atom isotope effects. Consequently, one would have to work with incomplete and uncertain guidelines, and the result would necessarily be an ad hoc procedure that would detract from the generality and predictive value of the Bebovib model.

We recognize the persuasiveness of the evidence that led to the incorporation of isotope effects for allyl radical formation in the algorithm for estimating extents of bond making and bond breaking, but we are not completely convinced that the approach is valid. That the migrating allyl group, even in a loose transition structure, must possess force constants similar to a significant extent to those of a free allyl radical is not necessarily a self-evident proposition. Even if it does, the proper algorithm for describing the amount of radical character of a given transition structure is highly uncertain.

The Gajewski, Olson, and Tupper paper does not mention the 2-(methoxycarbonyl) derivative, implying that they see no need for revision of previous conclusions.²⁷ The conclusions from the secondary deuterium isotope effects were that there was approximately 30% bond breaking and 30% bond making in the transition structure. Table 5 shows that the only viable models are those with complete or nearly complete conservation of bonding, which would argue against any significant radical character in the migrating allyl group. The best fit is for $n(\text{CO})$ 0.6 and $n(\text{CC})$ 0.4, but models with $n(\text{CO})/n(\text{CC})$ of 0.7/0.3 and 0.6/0.3 fit both deuterium and heavy-atom KIE at least as well as the best fits achieved with the 2-(trimethylsilyloxy) derivative. One can thus conclude that both bond breaking and bond making amount to 30–40%, in excellent agreement with the previous conclusions.

A referee has requested further detail on the models. To the extent possible, bond orders to each atom of the cyclic system were conserved. This was achieved in the case of the best model for the methoxycarbonyl derivative, where bond changes are synchronous. It was obviously not possible in the case of the trimethylsilyloxy derivative, where bond breaking is far ahead of bond making. In this case, the bonding deficiency was allotted to the atoms of the breaking bond, O₃ and C₄, with total bond orders of 1.4 and 3.4, respectively. Bonding to all other atoms was conserved. The low bond order total to C₄ was required to match the rather large carbon isotope effect. Curvature parameters (eq 3) corresponding to quite low reaction coordinate frequencies were necessary to match the observed isotope effects. Because different models were used for different patterns of isotopic substitution (vide supra), it is not possible to specify unique reaction coordinate frequencies for the successful models, but most were in the range 100–300i cm⁻¹. As a result, tunnel corrections were negligibly small.

Experimental Section

Solvents (except NMR grade CCl₄) were dried immediately before use. Tetrahydrofuran (THF) was distilled from sodium and benzophenone; dichloromethane was distilled from P₂O₅; diisopropylamine, pyridine, and trichloromethylsilane (TMSCl) were distilled from CaH₂. Silica gel used for column chromatography was 60–200 mesh (Mallinckrodt 6581). Sodium [¹⁴C]acetates were purchased from ChemSyn Science Laboratories, and unlabeled compounds were from either Aldrich or Fluka.

Preparation of Labeled Allyl Acetate. Allyl acetate was prepared in CH₂Cl₂ solution by reaction of allyl alcohol (1.0 equiv) with acetyl chloride (1.1 equiv) in the presence of pyridine (1.2 equiv).^{10,11} [¹⁴C]Allyl alcohol¹⁴ was used for preparing [¹⁴C]allyl acetate, in 80% yield. [¹⁴C]-Allyl alcohol¹⁴ was used for preparing [¹⁴C]allyl acetate, in 69% yield. [¹⁴C]Acetyl chloride was used for preparing allyl [¹⁴C]acetate, in

90% yield. [¹⁴C]Acetyl chloride was used in preparing allyl [¹⁴C]-acetate, in 64% yield. The [¹⁴C]- and [¹⁴C]acetyl chlorides were prepared by reaction of the correspondingly labeled sodium acetate (appropriately diluted with sodium acetate) with phthaloyl chloride.²⁶ The ¹H NMR spectrum of each labeled allyl acetate was identical with that of the unlabeled ester. Each labeled ester was diluted with unlabeled ester so that the final activity was approximately 5 mCi/mol.

Rearrangement of 1a. The conditions used for carrying out the rearrangement of 2-(trimethylsilyloxy)-3-oxa-1,5-hexadiene (1a) were essentially those described in the dissertation of J. Emrani¹⁵ and reported briefly by Gajewski and Emrani.¹² Initially (runs 7–9), 1a was isolated by distillation¹⁵ and was used for rearrangement in THF solution. However, the isolated yields of 1a (see Table 1) were so low that the remaining rearrangements were carried out *in situ*, following the protocol that Gajewski and Emrani¹² used for measuring deuterium KIE with NMR spectroscopy. Isolation of labeled product (6) was carried out according to the procedure of Ireland and co-workers^{10,11} (Gajewski and Emrani¹² did not isolate product), but beyond that stage we found it necessary to convert 6 into its solid anilide for purifications suitable for ¹⁴C counting. An example of the complete procedure is described (run 3).

To a stirred solution of 3.0 g (30.0 mmol) of diisopropylamine in 20 mL of THF under argon, cooled to 0 °C in an ice-salt bath, was added 12.0 mL (30.0 mmol) of 2.5 N BuLi solution in hexanes. The solution was kept at <5 °C, and after 10 min the containing flask was attached to a diffusion pump line and the volatile compounds were removed at that low temperature. Fresh THF (20 mL) was distilled into the vessel onto the dry residue of lithium diisopropylamide (LDA), which dissolved on allowing the mixture to reach room temperature. The flask was again cooled in liquid N₂, and into it was distilled a measured aliquot (3.0 g, 30.0 mmol) of labeled allyl acetate that had been placed on the vacuum line earlier. After 5 min, 5.5 mL of TMSCl was distilled into the flask similarly. The flask was closed, and its contents were allowed to melt. The cold solution was stirred well, cooled again in liquid N₂, and again opened to the vacuum line, whereupon approximately half of the solvent was pumped off. A suspension remained that was kept at room temperature (22 °C) for 4 h, removed from the vacuum line, and filtered quickly. A small portion of the filtrate was set aside for 100% conversion. A sample of the remaining larger portion was taken for ¹H NMR measurement of conversion,²⁷ and the rearrangement in this portion was then stopped by addition of 5 mL of methanol. After standing 12 h this quenched rearrangement portion was mixed with 75 mL of 5% NaOH solution, and the mixture was extracted with 2 × 50 mL of ether. The alkaline solution was acidified with concentrated HCl, and the acidic solution was extracted with 3 × 50 mL of CH₂Cl₂ to remove 6. The dried (MgSO₄) CH₂Cl₂ solution was evaporated to give 378 mg (3.78 mmol) of crude 6, containing an impurity, assumed to be 2-(trimethylsilyloxy)-4-pentenoic acid. The crude acid was heated with 500 mg of aniline for 20 h at 140 °C in a sealed ampule. After being cooled the ampule was opened, the anilide was removed with 75 mL of ether, and the ether solution was washed successively with 2 × 50 mL of 2 N HCl and 4 × 50 mL of water and then dried over MgSO₄. Evaporation of the ether solution gave 372 mg of crude anilide. This was chromatographed on a column of silica gel with CH₂Cl₂ elution. An upper band remained on the column, and the eluate gave 347 mg (2.0 mmol, 53% of the 6) of 6-anilide. The product was sublimed under vacuum, crystallized from benzene/hexane, and sublimed again twice, giving mp 91.0 °C (lit.²⁸ mp 91.4–91.8 °C). This product was used for counting.

For 100% conversion, the smaller portion of the rearrangement filtrate was kept for 4 days in a stoppered flask and worked up in the same way to give 234 mg of crude anilide. Chromatography gave 210 mg of product (1.19 mmol, 54%) for further purification with crystallization and sublimation.

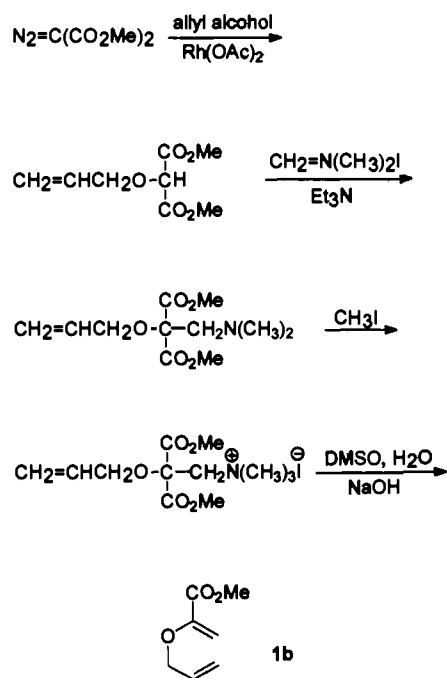
Preparation of 2-(Methoxycarbonyl)-3-oxa-1,5-hexadiene (1b). Compound 1b was prepared essentially by the method of Gajewski et al.,² shown in Scheme 2. Dimethyl diazomalonate, needed in the first step of Scheme 2, was prepared in 57% yield by the method of Lieber and

(26) Lawson, J. A.; Colwell, W. T.; DeGraw, J. I.; Peters, R. H.; Dehn, R. L.; Tanabe, M. *Synthesis* 1975, 29.

(27) The sample for ¹H NMR was pipetted into an NMR tube and rinsed with CDCl₃ into the tube. Integrations of the two doublets at δ 3.0 and 3.2 for —O—C(OTMS)=CH₂ in the enolate (1a), and of the multiplet at δ 2.2–2.4 for —CH₂CH₂— in the product (2a), were used. CHCl₃ (δ 7.24) in the CDCl₃ solvent was used as the NMR standard. Periodic integration of these signals shows that rearrangement at room temperature was virtually complete after 40 h.

(28) Roberts, J. D.; Mazur, R. H. *J. Am. Chem. Soc.* 1951, 73, 2509.

Scheme 2



co-workers.²⁹ For the chromatographic isolation of 1-[bis(methoxycarbonyl)methoxy]-2-propene and 1-[bis(methoxycarbonyl)((dimethylamino)methyl)methoxy]-2-propene, silica gel and elution with 1:1 diethyl ether/hexane was used. Chromatographic purification of **1b** was carried out on neutral alumina with the same eluant. The overall yield of **1b** from the dimethyl diazomalonnate step was 51%. For preparing [1-¹⁴C]**1b**, [2-¹⁴C]**1b**, [4-¹⁴C]**1b**, and [6-¹⁴C]**1b** we used, respectively, Eschenmoser's salt labeled in the methylene group,¹⁸ dimethyl [2-¹⁴C]diazomalonnate, [1-¹⁴C]allyl alcohol,¹⁴ and [3-¹⁴C]allyl alcohol.¹⁴ The labeled **1b** that were used for rearrangement had activities in the range 4–8 mCi/mol.

Dimethyl [2-¹⁴C]Diazomalonnate was prepared according to Scheme 3. A commercially available solution (0.5 mL, 2.45 mCi) of sodium [2-¹⁴C]-acetate was added to 2.44 g of sodium acetate, and the mixture was dried under vacuum. The dried salt was then used as in Scheme 3 with procedures from the literature.^{30–32} Dimethyl [2-¹⁴C]diazomalonnate was obtained in 9.3% overall yield and with activity 4.1 mCi/mol. It was converted into [2-¹⁴C]**1b** (Scheme 2).

Rearrangement of 1b. A solution of 926 mg (6.52 mmol) of **1b** was made in 30 mL of CCl₄ (NMR grade). Six milliliters was withdrawn and sealed in a snap-neck ampule for 100% conversion. The remaining

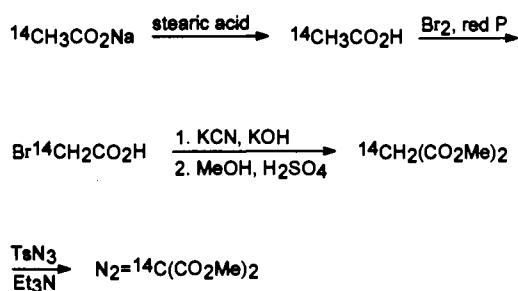
(29) Lieber, E.; Oftedahl, E.; Rao, C. N. R. *J. Org. Chem.* **1963**, *28*, 194.

(30) Liedtke, B.; Vollmer, K.-O. *J. Labelled Compd. Radiopharm.* **1978**, *14*, 825.

(31) Fitzell, D. L.; Hsieh, D. P. H.; Reece, C. A.; Seiber, J. *J. Labelled Compd. Radiopharm.* **1975**, *11*, 135.

(32) Bak, B. *J. Labelled Compd.* **1968**, *4*, 22.

Scheme 3



24 mL was sealed similarly for low conversion. The ampules had earlier been soaked overnight in KOH/ethanol solution, washed thoroughly, and dried at 120 °C.

Low Conversion. An example of the procedure is given. The sealed ampule was placed in an oven thermostatically controlled at 80 °C and was removed after 4 h 25 min. The ampule was cooled quickly and opened, and the CCl₄ was evaporated. A sample of the liquid residue was used for assay by ¹H NMR spectroscopy and showed that 26% conversion into **2b** had occurred. Assay of **1b** was used by integrating the multiplet for CH₂=CHCH₂O— at 4.3 ppm and of **2b** by integrating the triplet for O=CCH₂CH₂— at 2.9 ppm. Then, all of the reaction mixture was stirred for 1.5 h with a solution of 0.5 g of semicarbazide hydrochloride and 0.75 g of sodium acetate in 20 mL of water. The solution was diluted with 30 mL of water and was extracted with CHCl₃ to remove unreacted **1b** and the semicarbazone of **2b**. The CHCl₃ solution was dried over MgSO₄ and was evaporated to small volume under reduced pressure. Diethyl ether was added to precipitate the semicarbazone, which was filtered off and dried in air, giving 213 mg (1.07 mmol, 79% based on 26% conversion) of product. The semicarbazone was sublimed twice for scintillation counting. The filtrate of CHCl₃/ether was concentrated and placed on a column of neutral alumina, from which 453 mg (3.19 mmol, 83% based on 26% conversion) of **1b** was obtained.

100% Conversion. The 6-mL aliquot of CCl₄ solution was heated at 80 °C for 4 days. ¹H NMR spectroscopy showed that conversion was complete. Workup as described gave 224 mg (1.13 mmol, 87%) of semicarbazone.

KIE Measurements. A sample of approximately 3–8 mg of 6-anilide or **2b**-semicarbazone was weighed precisely (±0.002 mg) on a Cahn balance and was dissolved in 15 mL of cocktail (ICN Universal). Four samples were weighed for each run, and each sample was counted 30 times (three times per cycle for 10 cycles) on a Beckman Instruments scintillation counter, model LS 5000 TD, with 2σ at 0.5%. Three runs of low and 100% conversion were made for each of the labeled **1a** and **1b**. KIE were calculated in a standard way^{3,21,33} and are listed in Tables 2 and 3.

Acknowledgment. We thank the National Science Foundation (Grants CHE-9313657 and CHE-8919768) and the Robert A. Welch Foundation (Grant D-028) for support.

(33) Barry, B. A. *Errors in Practical Measurement in Science, Engineering and Technology*; Wiley: New York, 1978; p 75.