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The Benzidine and Diphenyline Rearrangements Revisited. 1-^{14}C and 1,1′-$^{13}C_2$ Kinetic Isotope Effects, Transition State Differences, and Coupled Motion in a 10-Atom Sigmatropic Rearrangement

Witold Subotkowski,[1] Lidia Kupczyk-Subotkowska, and Henry J. Shine*

Contribution from the Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, Texas 79409

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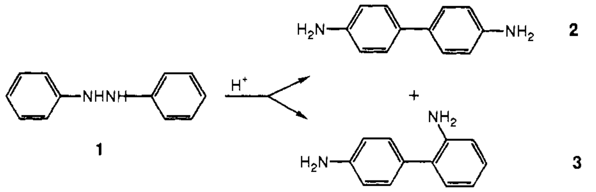
Abstract: KIE were measured for 1-^{14}C- and 1,1′-$^{13}C_2$-labeling in the acid-catalyzed rearrangement of hydrazobenzene (**1**) to benzidine (**2**) and diphenyline (**3**). Small KIE were found for forming **2**, but none were found for the formation of **3**. The results are consistent with concerted formation of **2** and nonconcerted formation of **3**. KIE were remeasured for 4-^{14}C-, 4,4′-$^{13}C_2$-, and ^{15}N,^{15}N′-labeling and were found to differ in magnitude from KIE reported earlier. The results are, nevertheless, consistent with the concerted formation of **2** and nonconcerted formation of **3**. The differences in transition states for these two processes are discussed. Quantitative measurements of product distributions gave 85% **2** and 15% **3**.

Introduction

The mechanism of the acid-catalyzed rearrangements of hydrazobenzene and its homologues was a "cause celebre" in organic chemistry for many years. The question of whether rearrangements were concerted or went through π-complex intermediates remained unresolvable until measurements of heavy-atom kinetic isotope effects (KIE) were made. In 1982, H.J.S. reported the nitrogen and carbon KIE for the rearrangement of hydrazobenzene (**1**), the prototype of the class. Rearrangement of **1**, which is kinetically first order in **1** and second order in acid,[2] gives mainly two products, benzidine (**2**), from which the class name is derived, and diphenyline (**3**) (eq 1). It was deduced from the heavy-atom KIE that formation of **2** was a concerted [5,5]-sigmatropic shift. In contrast, formation of **3** was found not to be concerted; that is, it followed the dictates of orbital-symmetry control for a [3,5]-sigmatropic shift.[3] Thereafter, measurements of KIE for other types of acid-catalyzed and thermal benzidine rearrangements followed, and all were found to fit into the expected pattern for sigmatropic processes.[4–11]



(1)

In principle, the motions of all of the atoms in a pericyclic process are coupled. Consequently, KIE should be experienced at atoms in the pericyclic array that are not directly involved in bond-breaking and bond-forming. Recently, we validated this principle in the Claisen rearrangement of allyl phenyl ether by measuring ^{14}C KIE at the 1-position of the ring and the β-position of the allyl group.[12] We have since then measured analogous KIE in the rearrangements of allyl vinyl ether[13] and its 2-(trimethylsilyl)oxy and 2-methoxycarbonyl derivatives.[14] With this principle in mind, we turned to the formation of benzidine from hydrazobenzene to find if KIE would result from labeling the 1,1′-positions of the hydrazobenzene. We had reported KIE earlier for labeling nitrogen atoms and the ortho and para positions of **1**,[3,11] but we felt now that it would be advisable to remeasure the nitrogen and para-carbon KIE so that a basis of contemporary data could be established for comparison with the planned measurement of KIE at the 1,1′-positions. Measurement of the new and remeasurement of the earlier-reported KIE for the benzidine rearrangement required also that the entire procedure for the isolation of the two products (**2** and **3**) be repeated, and this caused us to measure the relative amounts of **2** and **3** that are formed. Further, in the earlier work,[3] the KIE were obtained by measuring mass abundances in **2** and **3** themselves, and the quadrupole mass spectrometer measurements were made on samples sent to the laboratory of an early collaborator. In the ensuing years we found it better in benzidine rearrangements to make mass abundance measurements on the trifluoroacetyl derivatives of products and, furthermore, were able to do so with our own subsequently-acquired mass spectrometer. Therefore, we will now report on the ratio of the products **2** and **3**, the ^{15}N,^{15}N′, 1-^{14}C, 1,1′-$^{13}C_2$, 4-^{14}C, and 4,4′-$^{13}C_2$ KIE in their formation, and the difference in transition states that the KIE indicate.

Results and Discussion

The sources of the carbon label for preparing [1-^{14}C]**1** and [1,1′-$^{13}C_2$]**1** were [2-^{14}C]- and [2-^{13}C]acetone, respectively. These

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Table I. KIE for the Formation of Benzidine (**2**) and Diphenyline (**3**) from the Acid-Catalyzed Rearrangement of Hydrazobenzene (**1**)[a]

			KIE	
run no.	F^b	isotope position	**2**	**3**
1	0.26	1,1′-$^{13}C_2$[c]	1.0035 ± 0.0017	1.0001 ± 0.0049
2	0.15		1.0029 ± 0.0018	1.0007 ± 0.0042
3	0.12		1.0040 ± 0.0016	0.9990 ± 0.0044
4	0.20	1-^{14}C	1.0033 ± 0.0020	
5	0.17		1.0058 ± 0.0028	0.9930 ± 0.0015
6	0.10		1.0053 ± 0.0039	1.0037 ± 0.0020
7	0.30		1.0061 ± 0.0045	0.9998 ± 0.0043
8	0.22	4,4′-$^{13}C_2$[c]	1.0123 ± 0.0017	1.0018 ± 0.0018
9	0.18		1.0136 ± 0.0023	1.0012 ± 0.0017
10	0.16		1.0122 ± 0.0019	1.0002 ± 0.0021
11	0.19	4-^{14}C	1.0137 ± 0.0016	
12	0.22		1.0123 ± 0.0011	0.9992 ± 0.0014
13	0.18		1.0102 ± 0.0014	1.0027 ± 0.0013
14	0.22	^{15}N, $^{15}N'$[c]	1.0380 ± 0.0012	1.0352 ± 0.0021
15	0.18		1.0435 ± 0.0016	1.0379 ± 0.0031
16	0.15		1.0414 ± 0.0016	1.0370 ± 0.0043

[a] In 75% aqueous ethanol at 0 °C, 0.1 M HCl, 0.3 M LiCl. [b] Conversion. [c] For two atoms.

Table II. Summary of Averaged KIE

	KIE	
isotope position	**2**	**3**
1,1′-$^{13}C_2$[a]	1.0035 ± 0.0010	1.0000 ± 0.0026
1-^{14}C	1.0051 ± 0.0017	0.9988 ± 0.0017
4,4′-$^{13}C_2$[a]	1.0127 ± 0.0011	1.0011 ± 0.0011
4-^{14}C	1.0121 ± 0.0008	1.0010 ± 0.0010
^{15}N, $^{15}N'$[a]	1.0410 ± 0.0009	1.0367 ± 0.0009

[a] For two atoms.

were converted into [1-^{14}C]- and [1-^{13}C]-4-nitrophenol in the customary way.[15] Each labeled 4-nitrophenol was converted into labeled azobenzene, which was reduced to hydrazobenzene (**1**) as needed. The several procedures have been described earlier.[3] Rearrangement of **1** was carried out at 0 °C in 75% aqueous ethanol that was 0.016 M in **1**, 0.1 M in HCl, and 0.3 M in LiCl.[3] The times of quenching the reaction for low conversions were calculated from the rate constant reported earlier,[16] and these are listed in Table III; the reaction was allowed to run for 48 h for total conversion.

KIE Measurements. Both 2 and 3 were converted, after isolation and purification, into their bis(trifluoroacetyl) derivatives. Each derivative was first sublimed, then recrystallized, and again sublimed either two or three times for scintillation counting (^{14}C) and SIM quadrupole mass spectrometry (^{13}C and ^{15}N). A list of all runs is given in Table I and summarized in Table II.

The results in Table II for labeling at the 4- and 4,4′-positions show once again that formation of **2** is concerted, whereas formation of **3** is not. That is, there are substantial carbon KIE for **2** but, within experimental error, none for **3**. The results for 2 differ in magnitude from those reported earlier, however. That is, for 4-^{14}C- and 4,4′-$^{13}C_2$-labeling, the earlier KIE were 1.0284 and 1.0209, respectively.[3] We place greater reliance on the new results for three reasons. First, bis(trifluoroacetyl) derivatives were used. They are more easily purified and stored than **2** and **3** themselves. Diphenyline (**3**), furthermore, is usually obtained as an oil and is very difficult to keep as a solid. Second, unlike **2** and **3**, the bis(trifluoroacetyl) derivatives do not give rise to M − 1 peaks in their mass spectra, a feature that makes computation of isotopic abundances simpler and more accurate. Consequently, the new scintillation counting and mass spectrometric data are regarded as being more reliable than the earlier data. Third, the theoretical logarithmic ratio (eq 2)[17] for labeling

$$\frac{\ln(k(^{12}C)/k(^{14}C))}{\ln(k(^{12}C)/k(^{13}C))} \simeq 1.9 \qquad (2)$$

at one atom is obeyed by the present results (ratio 1.9) but not by the earlier (ratio 2.7).[18] The new nitrogen KIE also differ from the earlier ones, substantially. That is, whereas $k(^{14}N)/k(^{15}N)$ (for two atoms) for **2** and **3** were reported as 1.0222 and 1.0633, respectively,[3] they are now seen to be closely similar and approximately 4%. The difference in results stems probably from unrecognized errors in the earlier mass spectrometric measurements, attributable, we believe, to the relative difficulty of working with **2** and **3** themselves and, in particular, with **3** as an oil.

Labeling at the 1- and 1,1′-positions of **1** resulted in small but definite KIE for the formation of **2**. In contrast, no 1- and 1,1′-KIE were found for the formation of **3**. As far as the KIE for **2** are concerned, they are so small that our precision is poor. The data do not fit the logarithmic ratio (eq 2) well, giving a value of 2.9 for single-atom labeling. With our current instrumentation it is doubtful that we could improve on our precision. The results, however, tell us that the 1,1′-atoms are in motion in the transition state for forming **2**. This is what one would expect for the concerted formation of **2** in its 10-atom pericyclic array. Thus, in this case, as in those noted above,[12-14] our experimental data uncover the coupled motion of atoms in a pericyclic reaction. Analogous motion of the carbon atoms in the formation of **3** is not detectable. In fact, the only atoms in motion in reaching the transition structure for **3** are shown to be the nitrogen atoms. Thus, under the conditions we have used, 15% of the molecules of **1** undergo N–N bond scission and the separated halves rejoin intramolecularly, but not in a pericyclic way. The similarity in the magnitudes of the nitrogen KIE for forming **2** and **3** is striking in view of the fact that the two products are formed along different pathways. Thus, the extent of breaking the N–N bond differs little from one pathway to the other, by the time the respective transition structures are reached. Further, the small sizes of the carbon KIE indicate that even though formation of **2** is concerted, the 1,1′-carbon atoms do not contribute much to motion along the reaction coordinate. Our KIE have allowed us to define more clearly the differences in transition states for the two rearrangements. Unfortunately, still, they do not tell us why protonated **1** leads to both of these distinctly different transition states and how, exactly, that for **3** finally leads to **3**.

The Products of Rearrangement. A mixture of azobenzene (from the applied air oxidation of unrearranged **1**), **2**, and **3** was obtained from a low-conversion reaction. This mixture was separated into its components by a sequence of extraction, precipitation, and column chromatography as described in detail in the Experimental Section. A significant (ca. 15–20% in most runs) loss in products ensued. In the total-conversion runs, the components of the product mixture were a small amount of azobenzene, **2**, and **3**. Losses in these cases amounted to 5–10%. The data are listed in Tables III and IV. Crude **2** was crystallized from hot water while **3** was obtained as an oil after column chromatography. Tables III and IV report the ratio **2**:**3** after these purifications. In each case the ratio is quite different from that (70:30) which has become the accepted norm for rearrangement of **1**. That is, the ratio **2**:**3** from low conversions averages 5.3 ± 0.6, while from total conversions the average is 5.4 ± 0.4. In these experiments, therefore, the yields of **2** and **3** approximate 84 and 16% rather than 70 and 30%. Even if the amounts of crude **2** (Table IV) were used instead of the yields after crystallization, the relative yields of the two products would hardly be different (i.e., 86 and 14%).

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Table III. Products of Rearrangement of Hydrazobenzene (**1**) into Benzidine (**2**) and Diphenyline (**3**): Low Conversions[a]

		conversion[b]			amt of product, mmol (%)						
run no.	time, min	F_1	F_2	F_3	A^c	B^d	C^e	D^f	sum[g]	B/D	C/D
1	30	0.25	0.22	0.19	5.38 (66.0)	1.56 (19.1)	1.29 (15.8)	0.26 (3.2)	88.3	6.00	4.96
2	20	0.15	0.13	0.13	5.95 (73.0)	0.89 (10.9)	0.74 (9.1)	0.16 (2.0)	85.9	5.56	4.63
3	15	0.14	0.12	0.10	6.86 (84.2)	0.83 (10.2)	0.71 (8.7)	0.14 (1.7)	96.1	5.93	5.07
4	30	0.24	0.21	0.19	5.40 (66.3)	1.42 (17.4)	1.25 (15.3)	0.29 (3.6)	87.2	4.90	4.31
5	25	0.21	0.18	0.16	5.49 (67.4)	1.25 (15.3)	1.05 (12.9)	0.20 (2.5)	85.2	6.25	5.25
6	20	0.13	0.10	0.13	5.61 (68.8)	0.72 (8.8)	0.59 (7.2)	0.11 (1.3)	79.0	6.55	5.36
7	40	0.35	0.34	0.25	5.21 (63.9)	2.42 (29.7)	1.96 (24.0)	0.36 (4.4)	98.0	6.72	5.44
8	30	0.24	0.22	0.19	5.60 (68.7)	1.56 (19.1)	1.30 (16.0)	0.25 (3.1)	90.9	6.24	5.20
9	25	0.20	0.18	0.16	5.83 (71.5)	1.27 (15.6)	1.02 (12.5)	0.19 (2.3)	89.4	6.68	5.37
10	20	0.18	0.16	0.13	5.94 (72.9)	1.13 (13.9)	0.93 (11.4)	0.19 (2.3)	89.1	5.95	4.89
11	26	0.21	0.19	0.17	5.65 (69.3)	1.31 (16.1)	1.04 (12.8)	0.23 (2.8)	88.2	5.70	4.52
12	30	0.24	0.22	0.19	5.54 (68.0)	1.58 (19.4)	1.30 (16.0)	0.19 (2.3)	89.7	8.32	6.84
13	25	0.21	0.18	0.16	5.51 (67.6)	1.29 (15.8)	1.01 (12.4)	0.16 (2.0)	85.4	8.06	6.31
14	30	0.25	0.22	0.19	5.56 (68.2)	1.57 (19.3)	1.31 (16.1)	0.25 (3.1)	90.6	6.28	5.24
15	25	0.20	0.17	0.16	5.67 (69.6)	1.20 (14.7)	1.09 (13.4)	0.21 (2.6)	86.9	5.71	5.19
16	20	0.17	0.15	0.13	6.04 (74.1)	1.04 (12.8)	0.97 (11.9)	0.18 (2.2)	89.1	5.78	5.39

[a] 8.15 mmol of **1** was used in each run. [b] $F_1 = (B + D)/(A + B + D)$; $F_2 = (B + D)/8.15$; F_3 from the time elapsed and the rate constant $k = 7.0 \times 10^{-3}$ min^{-1}.[15] [c] Recovered azobenzene. [d] Crude **2** from precipitation plus column chromatography. [e] **2**, after crystallization from water. [f] **3**, from column chromatography. [g] $100(A + B + D)/8.15$.

Table IV. Products of Rearrangement of Hydrazobenzene (**1**) into Benzidine (**2**) and Diphenyline (**3**): Total Conversions[a]

run	amt of product, mmol (%)			$(B + D)$,		
no.	B^b	C^c	D^d	%	B/D	C/D
1	1.26 (77.3)	1.09 (66.9)	0.21 (12.9)	90.2	6.00	5.19
2	1.28 (78.5)	1.06 (65.0)	0.20 (12.3)	90.8	6.40	5.30
3	1.28 (78.5)	1.14 (69.9)	0.24 (14.7)	93.3	5.33	4.75
4	1.23 (75.5)	1.10 (67.5)	0.22 (13.5)	89.0	5.59	5.00
5	1.12 (68.7)	1.09 (66.9)	0.23 (14.1)	82.8	4.87	4.74
6	1.15 (70.6)	1.10 (67.5)	0.22 (13.5)	84.0	5.23	5.00
7	1.24 (76.1)	1.04 (63.8)	0.19 (11.7)	87.7	6.53	5.47
8	1.82 (74.3)	1.74 (71.0)	0.29 (11.8)	86.1	6.28	6.00
9	2.11 (86.1)	1.80 (73.5)	0.32 (13.1)	99.2	6.59	5.63
10	2.01 (82.0)	1.64 (66.9)	0.28 (11.4)	93.5	7.18	5.86
11	1.31 (80.4)	1.05 (64.4)	0.20 (12.3)	92.6	6.55	5.25
12	2.11 (86.1)	1.60 (65.3)	0.30 (12.2)	98.4	7.03	5.33
13	2.21 (90.2)	1.76 (71.8)	0.31 (12.7)	102.9	7.13	5.68
14	2.04 (83.3)	1.76 (71.8)	0.30 (12.2)	95.5	6.80	5.87
15	2.05 (83.7)	1.70 (69.4)	0.32 (13.1)	96.7	6.41	5.31
16	2.10 (85.7)	1.84 (75.1)	0.32 (13.1)	98.8	6.56	5.75

[a] After 48 h. The amount of **1** used was 1.63 mmol in runs 1–7 and 11, while 2.45 mmol was used in runs 8–10 and 12–16. [b] Crude **2** from precipitation plus column chromatography. [c] **2**, after crystallization from water. [d] **3**, from column chromatography.

The ratio 70:30 for **2**:**3**, was first reported by Carlin and co-workers in 1951,[19] and was determined by UV-spectroscopic analysis of **1**–**3** in solution after rearrangement had been quenched. The same distribution is quoted (without citation) by Ingold and Hughes in their first summary of the mechanism of the benzidine rearrangement.[20] Hammond and Grundemeier used Carlin's method of analysis for rearrangements in absolute ethanol and arrived at ratios also averaging 70:30.[21] Banthorpe and co-workers measured the yields of **2** and **3** from rearrangements in 60% aqueous dioxane, aqueous ethanol, and anhydrous ethanol, using a combination of Carlin's spectroscopic analysis and gravimetric (for benzidine sulfate) assay. They arrived at 72–76% **2** and 24–28% **3**.[22] On the other hand, Vecera and co-workers obtained relatively smaller amounts of **3**, the ratio **2**:**3** varying between 3.3 and 5.3, depending on the solvent and acidity. In 50% ethanol and 0.1 M HCl at 20 °C, they obtained a ratio of 5.3:1. UV spectroscopy was the method of analysis.[23] It seems, therefore, that the ratio of yields that is usually quoted (70% **2** and 30% **3**) may not be as invariant as has often been thought. The data in Tables III and IV are not in accord with that ratio. Further, analysis of a mixture of bis(trifluoroacetyl) derivatives (TFA-2 and TFA-3) obtained from a total-conversion run gave a ratio of 5.3 with ^1H NMR analysis and 5.5 with GC analysis.

Experimental Section

[2-^{13}C]Acetone, 99%, was obtained from Cambridge Isotope Laboratories; [2-^{14}C]acetone, 1.7 mCi/mmol, was obtained from Amersham. Labeled acetone was converted into 4-nitro-1-labeled-phenol[15] which was converted into 1-labeled-aniline as described earlier.[10] The aniline was oxidized with MnO_2 to [1-^{14}C]azobenzene and, as appropriate, [1,1′-$^{13}C_2$]azobenzene. In the former case, dilutions with unlabeled acetone gave a final product with an activity of 7 mCi/mol. In the latter case, dilution with azobenzene only was used. After chromatography on alumina and sublimation, the product was found with SIM mass spectrometry to contain 7.6% [1,1′-$^{13}C_2$]azobenzene.

Rearrangement of 1. Low Conversion. **1** (2.2 g) was obtained by reduction of 2.4 g of azobenzene in 150 mL of acetone with 12 g of Zn powder and 15 mL of saturated NH_4Cl solution. After being dried for 12 h over $CaCl_2$ and under vacuum, 1.5 g (8.15 mmol) of **1** was dissolved in a mixture of 306 mL of freshly distilled 95% EtOH and 102 mL of water. Another solution was prepared of 10.5 g (248 mmol) of LiCl in a mixture of 41 mL of 2.0 N HCl and 61 mL of water. Each solution was cooled to 0 °C under argon. The two solutions were mixed under a flow of argon and kept at 0 °C for 30 min, after which 50 mL of saturated KOH solution was added quickly. Air was bubbled through the alkaline solution for 24 h to oxidize unused **1** to azobenzene. The solution was evaporated to smaller volume at room temperature. Approximately 10 mg of azobenzene codistilled in the evaporation. The mixture that remained was extracted with 4 × 100 mL of ether. The ether solution was washed with 3 × 100 mL of 2 N HCl and 2 × 50 mL of water. The dried ($MgSO_4$) ether solution was evaporated in a rotary evaporator to give 1015 mg (5.58 mmol, 68.5%) of azobenzene. This was sublimed to give 989 mg (5.38 mmol, 66%) of azobenzene. The combined aqueous washings was made alkaline with saturated KOH solution and was extracted with 3 × 100 mL of ether. Workup gave 379 mg of residue. This was dissolved in 8 mL of CH_2Cl_2, and hexane was added slowly to the solution to precipitate 210 mg of **2**, mp 125–126 °C. After filtration, the solution was evaporated to give 126 mg of residue. This was chromatographed on silica gel (Baker 230–400 mesh, for flash chromatography) with 5:1 cyclohexane/absolute EtOH to give 11 mg of unknowns (two or more), 47.6 mg (0.26 mmol, 3.2%) of **3** as an oil, and 77.6 mg of **2**, mp 125-126 °C. The two portions of **2** were combined and crystallized from hot water to give 237 mg (1.29 mmol, 15.8%) of **2**, mp 125–126 °C. This (**2**) was dissolved in 15 mL of benzene to which was then added 1.0 mL of trifluoroacetic anhydride. After 2 h the solution was evaporated to give 449 mg (1.29 mmol) of *N*,*N*′-bis(trifluoroace-

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tyl)benzidine (TFA-2). Sublimation gave 312 mg, mp 325–326 °C. **3** was treated similarly to give 91.5 mg (0.26 mmol) of *N,N'*-bis(trifluoroacetyl)diphenyline (TFA-3), mp 173–174 °C. For KIE measurements, each derivative was next crystallized from acetone/hexane and sublimed two (^{13}C and ^{15}N) or three (^{14}C) times. Details on yields are given in Table III.

Table III lists three conversions, F_1–F_3, identified in footnote *b*. For the calculation of KIE, the average of these three was used.

Total Conversion. The procedure was as described above but with a smaller amount of **1** (see Table IV). The rearrangement mixture was kept in the refrigerator for 48 h and then made alkaline. Treatment with air was omitted. Details of yields are given in Table IV.

The Ratio 2:3. This ratio, derived from isolated products, is listed for each run in Tables III and IV. The ratio was determined also in two other ways with unlabeled materials, each carried out with the bis(trifluoroacetyl) derivatives, as follows.

With ^{1}H NMR Analysis. The ^{1}H NMR spectrum of pure TFA-2 has two multiplets (for an A,A',B,B' system) at 7.85 and 7.72 ppm. The spectrum of TFA-3 has multiplets in the ratio 2:1:5 at 7.81, 7.65, and 7.43 ppm. In the ^{1}H NMR spectrum of a mixture of TFA-2 and TFA-3, therefore, the signal for the 5 H of TFA-3 at 7.43 ppm remained distinct, whereas the remaining signals for 3 H (at 7.81 and 7.65 ppm) overlapped those of the 8 H of TFA-2. A solution of 5.55 mg of TFA-2 and 1.02 mg of TFA-3 (ratio 5.44:1) was prepared. From integration of the appropriate multiplets over the spectrum widths 7.962–7.619 and 7.539–7.332 ppm, it was calculated that the ratio of derivatives was 5.3:1. When the analysis was applied to an unknown mixture of the derivatives from a high-conversion rearrangement, the ratio obtained was also 5.3:1.

With GC Analysis. Both the known and unknown mixtures described above were assayed on a 4-ft × $^1/_8$-in. stainless steel column of OV-101 on 80–100 mesh Chrom WHP. Three assays were made in each case and gave, for both the known and unknown mixtures, a ratio of (5.5 ± 0.1):1. In the GC spectrum of the mixture from rearrangement of **1**, three other small peaks were detected.

Measurements of KIE. ^{13}C KIE were calculated from the relative abundances of peaks at *m/z* 378 and 376 for the purified samples of TFA-2 and TFA-3. The SIM mode of a Hewlett-Packard Model 5995 mass spectrometer was used. Five or six runs per sample were made, each consisting of 1500-2500 scans. The data were normalized with similar measurements on unlabeled TFA-2 and TFA-3. The relative abundances were treated statistically in 25 blocks of scans, as described earlier.[7] KIE were calculated with eq 3.

^{14}C KIE were measured with scintillation-counting data. An approximately 2-mg sample was weighed precisely (±0.001 mg) on a Cahn balance and dissolved in 2 mL of acetone. To the solution was added 10 mL of cocktail (ScintiLene BD, Fisher BP 455-5). The TFA samples were not soluble in the cocktail alone. Four replicates of each sample were counted, each 30 times, with $2\sigma < 0.50\%$. The mean value of all counts was used in eq 3, where F = conversion, A_F = either (M + 2)/M

$$\mathrm{KIE} = \log(1 - F)/\log((1 - F)(A_F/A_0)) \qquad (3)$$

or the counts per milligram at conversion F, and A_0 = either (M + 2)/M or counts per milligram at total conversion.

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