Reorientation and Transalkylation Reactions of Isotopically Labeled Toluene, Ethylbenzene, and *n*-Propylbenzene[1]

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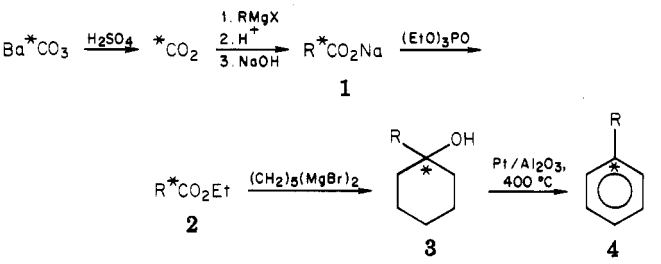
Toluene-*1*-^{13}C was treated with Al_2Br_6 and HBr neat and in 1,2,4-trichlorobenzene solution at 35 °C. Aliquot samples of the reaction mixtures were taken at time intervals from 15 min to 8 days; toluene was recovered by GC and the distribution of ^{13}C in the ring was determined by quantitative ^{13}C NMR analysis. The reorientation of the methyl group with respect to the ^{13}C-labeled carbon observed is best explained in terms of successive intramolecular 1,2-shifts, in agreement with previous ^{14}C work. Ethylbenzene-*1*-^{13}C was treated with Al_2Br_6 and HBr in 1,2,4-trichlorobenzene solution at 10 °C. Aliquot samples of the reaction mixture were taken after reaction times of from 30 s to 20 h and analyzed by GC for ethyl-, diethyl-, and triethylbenzene. Isolation of ethylbenzene from each sample was accomplished by preparative GC, and the distribution of ^{13}C in the ring was determined by quantitative ^{13}C NMR. A mixture of ethylbenzene-*1*-^{13}C and ethylbenzene-*8*-^{2}H was similarly treated with Al_2Br_6/HBr, and aliquot samples of the reaction mixture were analyzed as before. In addition, analysis for molecules of ethylbenzene labeled with both ^{13}C and ^{2}H was carried out by GC/MS. The reorientation of the ethyl group on the benzene ring with respect to the ^{13}C-labeled carbon was detected first in the para position, and only after diethylbenzene was produced. Doubly labeled molecules were produced at the same rate as the rate of appearance of ^{13}C in the para position. The results indicate that reorientation of ethyl group takes place predominantly by an intermolecular transalkylation–dealkylation mechanism. The reaction of *n*-propylbenzene-*1*-^{13}C with Al_2Br_6 and HBr in 1,2,4-trichlorobenzene solution at 10 °C was found to be very similar to that of ethylbenzene-*1*-^{13}C; the mechanism of isotopic reorientation is assumed to be the same as that of ethylbenzene-*1*-^{13}C.

Friedel–Crafts alkylation and disproportionation reactions often produce a high proportion of meta- and 1,3,5-oriented alkylated arenes, especially when aluminum halide catalysts are used in large amounts. These results have generally been explained in terms of either initial formation of 1,2,4-trialkylbenzenes followed by dealkylation or isomerization of initially formed 1,2- and/or 1,4-dialkylbenzenes.[2] Whereas the production of *m*-dialkylbenzenes from 1,2,4-trialkylbenzenes is necessarily intermolecular, the isomerization of 1,2- and/or 1,4-dialkylbenzenes might occur by either an intermolecular process or by an intramolecular 1,2-shift. The only case in which the isomerization of a dialkylbenzene can definitely be shown to be intramolecular is that of the xylenes, which have been demonstrated to undergo reorientation without the production of any toluene.[3,4] The intramolecular 1,2-shift of a methyl group was confirmed by the elegant work of Steinberg and Sixma with ^{14}C-ring-labeled toluene.[5] The isomerization of all of the higher dialkylbenzenes is accompanied by disproportionation; however, on the basis of kinetic and equilibrium studies, Allen and co-workers concluded that the isomerization of ethyltoluene is more than 84% intramolecular and less than 16% intermolecular.[6] Olah, Meyer, and Overchuk studied the isomerization of *o*-, *m*-, and *p*-diethylbenzenes by aluminum chloride, separately, and in the presence of benzene; they reported that their results could be best explained by a sequence of 1,2-shifts.[7] Wolf and his co-workers prepared ethylbenzene-*1*-^{14}C and treated it with aluminum bromide/hydrogen bromide.[8] After various reaction periods, the recovered ethylbenzene was degraded, and the distribution of the isotopic carbon was determined. In five experiments, the ^{14}C was found to be 18–25% in the para position, with respect to the ethyl group, and only 3–6% in the ortho and meta positions. This led Wolf to state that a 1,2-shift of an ethyl group in ethylbenzene is slow compared to an intermolecular transfer in a disproportionation reaction, which conflicts with the conclusions of Allen[6] and Olah.[7]

Scheme I[a]



[a] a, R = CH_3; b, R = CH_3CH_2; c, R = $CH_3CH_2CH_2$.

The isotopic distributions found by Wolf in his five reaction mixtures were in all cases high in the para position compared to the ortho and meta positions, but there was not a great difference between the distribution found after the shortest reaction period (7.5 min) and the longest reaction period (23 min). This led us to wonder if a pseudoequilibrium composition had not been produced even during the shortest reaction period and if more meaningful kinetic data might be obtained from still shorter reaction periods. The tremendous experimental simplification intrinsic to the use of ^{13}C-labeled substrates, with monitoring by NMR and mass spectrometry, appeared to us to offer the possibility of yielding definitive new information about the mechanisms of the reorientation and transalkylation reactions of ethylbenzene and its homologues. For example, it should be possible to follow any isotopic rear-

(1) (a) Paper 37. New Friedel–Crafts Chemistry. Paper 36: Roberts, R. M.; Elrod, L. W. *J. Org. Chem.* **1981**, *46*, 3732. (b) Generous support of this research by the Robert A. Welch Foundation is gratefully acknowledged.

(2) Price, C. C. "Organic Reactions"; Wiley: New York, 1946; Vol. 3, Chapter 1.

(3) Baddeley, G.; Holt, G.; Voss, D. *J. Chem. Soc.* **1952**, 100–105.

(4) McCaulay, D. A.; Lien, A. P. *J. Am. Chem. Soc.* **1952**, *74*, 6246–6250.

(5) Steinberg, H.; Sixma, F. L. J. *Recl. Trav. Chim. Pays-Bas* **1962**, *81*, 185–197.

(6) (a) Allen, R. H.; Yats, L. D.; Erley, D. S. *J. Am. Chem. Soc.* **1960**, *82*, 4853–4856. (b) Allen, R. H. *Ibid.* **1960**, *82*, 4856–4858.

(7) Olah, G. A.; Meyer, M. W.; Overchuk, N. A. *J. Org. Chem.* **1964**, *29*, 2313–2315.

(8) (a) Unseren, E.; Wolf, A. P. *J. Org. Chem.* **1962**, *27*, 1509–1513. (b) Moore, G. G.; Wolf, A. P. *Ibid.* **1966**, *31*, 1106–1110.

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Table I. Reaction of Toluene-1-^{13}C with Aluminum Bromide and Hydrogen Bromide at 35 °C[a]

time	% T[b]	% X[c]		distribution of ^{13}C in the ring[d]			
		meta + para	ortho	C_1	$C_{2,6}$ (ortho)	$C_{3,5}$ (meta)	C_4 (para)
0	100	0	0	0.67	0.17	0.11	0.05
15 min	100	0	0	0.59	0.24	0.12	0.05
30 min	99	trace	0	0.57	0.26	0.11	0.05
60 min	99	trace	0	0.53	0.31	0.11	0.05
90 min	99	trace	0	0.51	0.31	0.13	0.05
120 min	99	1	0	0.44	0.34	0.15	0.07
3 h	98	2	0	0.42	0.32	0.19	0.08
5 h	98	2	0	0.30	0.43	0.18	0.09
10 h	97	3	0	0.27	0.36	0.24	0.12
20 h	95	5	0	0.19	0.34	0.31	0.16
34 h	91	9	trace	0.18	0.30	0.32	0.20
48 h	88	12	trace	0.18	0.30	0.32	0.20
72 h	78	22	trace	0.16	0.34	0.31	0.19
5 days	66	33	1	0.16	0.32	0.33	0.19
8 days	59	33	4	0.16	0.31	0.34	0.19

[a] Molar ratio of toluene to aluminum bromide was 5:1, with an excess of hydrogen bromide. [b] Percentage of toluene. [c] Percentage of xylene. Although benzene was produced in all experiments in which xylenes were detected, its percentage is not included in the table. [d] Percentage of ^{13}C in each position of the toluene ring divided by the total percentage of ^{13}C in the toluene ring.

rangement of ethylbenzene-1-^{13}C almost continuously from the first few seconds of reaction by taking small samples of the reaction mixture at various time intervals and, after an appropriate workup, analyzing them by ^{13}C NMR spectrometry.[9] This paper reports the results of such experiments on toluene-1-^{13}C, ethylbenzene-1-^{13}C, and *n*-propylbenzene-1-^{13}C, as well as a specific test for an intermolecular mechanism of reorientation of ethylbenzene in which ethylbenzene-1-^{13}C and ethylbenzene-8-^{2}H were employed in the same reaction mixture.

The alkylbenzenes-1-^{13}C were synthesized by known procedures as outlined in Scheme I; details of modifications are described in the Experimental Section.

Results and Discussion

Toluene. Preliminary experiments were carried out by using toluene-1-^{13}C (**4a**) as the substrate.[10] The results presented in Table I show good agreement with those of Steinberg and Sixma.[5] The isotopic enrichment at C-1 diminished progressively toward one-sixth 1/6 of the total amount of enrichment, and it reached this equilibrium value between 48 and 72 h after the reaction began. The isotopic content increased first at the ortho positions, passing through a maximum at about 5 h and then decreasing to approach the statistical equilibrium value, whereas the isotopic contents of the meta and para positions showed steady increases toward the statistical values. We observed a slightly larger amount of intermolecular reaction (as evidenced by appearance of xylenes) than did Steinberg and Sixma, but not enough to play any significant role in the reorientation of the isotope, which clearly occurs by an intramolecular 1,2-shift mechanism.

The effect of an inert solvent, 1,2,4-trichlorobenzene, on the reaction of toluene with Al_2Br_6/HBr was investigated at 35 and at 50 °C. In the experiment at 35 °C the rate and pattern of reorientation were about the same, but the rate of transalkylation was slower than in the absence of solvent. In the experiment at 50 °C not only more xylenes but also appreciable amounts of trimethylbenzenes were observed. The rates of increase in ^{13}C content in the meta and para positions of the toluene ring were unchanged even after 10% of xylenes and 10% of trimethylbenzenes had formed, showing that the intermolecular transalkylation of toluene is too slow to play an appreciable part in the isotopic reorientation process.

Ethylbenzene. The results from an experiment in which ethylbenzene-1-^{13}C (**4b**) was treated with aluminum bromide and hydrogen bromide in 1,2,4-trichlorobenzene solution of 10 °C are depicted in Table II. First, it should be noted that more transalkylation occurred in 30 s at 10 °C than was observed for toluene in 2 h at 35 °C. The first increase in ^{13}C content occurred at the para position, another marked difference from the behavior of toluene-1-^{13}C; after 2 h the isotopic content there had tripled, while there was no increase of the isotopic content in the ortho and meta positions. As the reaction course was followed for 5 h, the ^{13}C isotopic content began slowly to increase in the ortho and meta positions as well, but it never caught up with the amount in the para position.

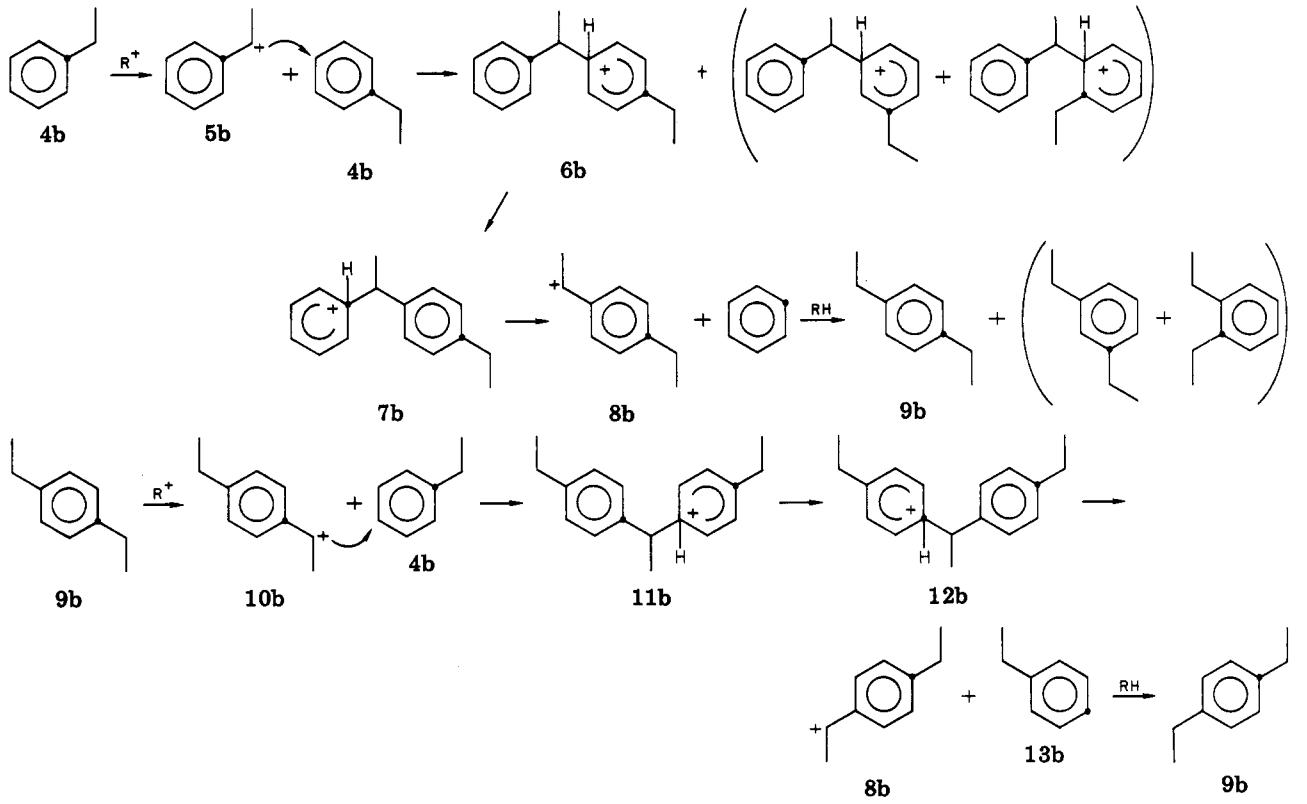
In contrast with the ^{14}C-label work,[8] it was possible to follow the course of the ^{13}C label reorientation virtually continuously from the beginning, so that there was no possibility of a rapid initial rearrangement to the ortho position going unobserved. Thus, our results not only agree with those of Wolf but they also extend them so as to exclude the possibility that an intramolecular 1,2-shift mechanism plays an important role in the isotopic reorientation of C(1)-labeled ethylbenzene. Rather, an intermolecular transalkylation–dealkylation mechanism is confirmed. A pathway for the formation of ethylbenzene-4-^{13}C by such a mechanism[11] is outlined in Scheme II. In the reorientation of the isotope in this way, the production of the para isomer is favored electronically over that of the meta at the stage where the substrate **4b** undergoes nucleophilic attack by the carbocation **5b**. Al-

(9) An examination of the elegant work of Wolf and his coworkers[8] will convince the reader of the prohibitive difficulty of a similar kinetic study in the ^{14}C-labeled system, wherein each determination of isotope distribution requires a tedious molecular degradation before a radioactive analysis, with a considerable margin of error.

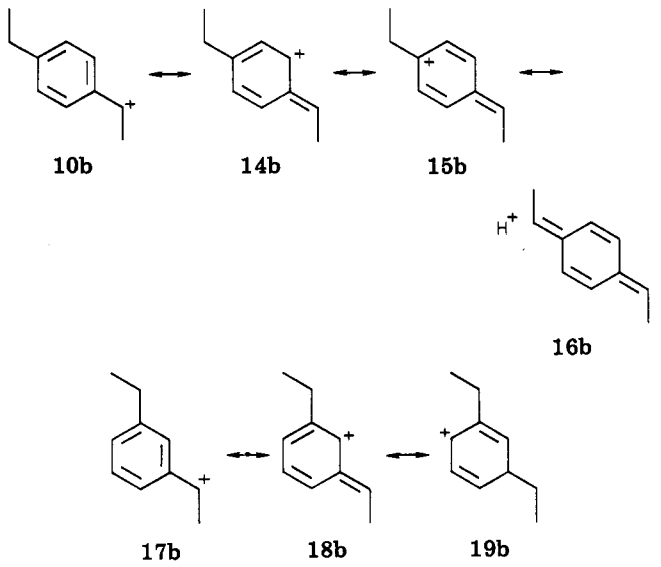
(10) It will be noted that the ^{13}C content in the ortho, meta, and para positions of the substrate "toluene-1-^{13}C" in Table I is significantly higher than the natural abundance value, and this is also true of the "ethylbenzene-1-^{13}C" and "*n*-propylbenzene-1-^{13}C" used as substrates. This is owing to the partial migration of the isotope around the ring during the synthesis of the substrate alkylbenzenes, as described in the Experimental Section and in footnote 19.

(11) (a) Pines, H.; Arrigo, J. T. *J. Am. Chem. Soc.* **1958**, *80*, 4369. (b) Streitwieser, A.; Reif, L. *Ibid.* **1964**, *86*, 1988. (c) Roberts, R. M.; Khalaf, A. A.; Greene, R. N. *Ibid.* **1964**, *86*, 2846. In Scheme II we have shown the production of ethylene-4-^{13}C (**13b**) by transalkylation between intermediate **10b** and starting material **4b**. Transalkylation between two molecules of **10b** to produce **13b** and a triethylbenzene is also possible, as are other transalkylations between di- and triethylbenzenes, but these are less probable in the early stages of the reaction.

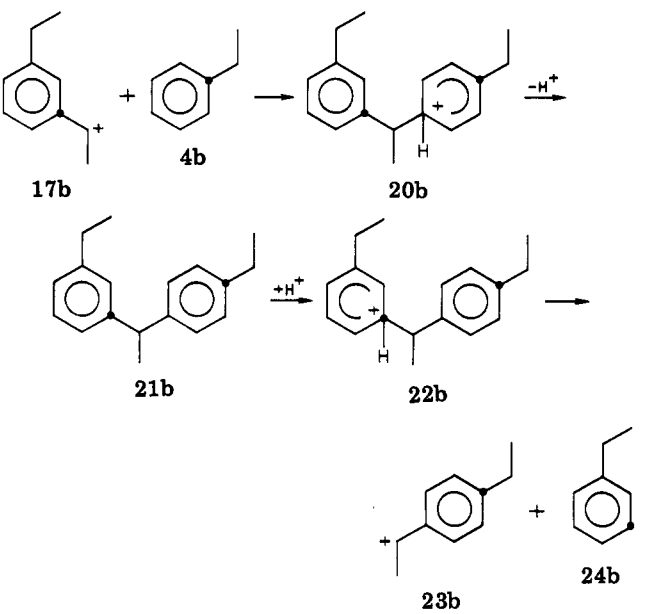
Scheme II



Scheme III



Scheme IV



though attack of the ortho position would also be favored electronically, presumably steric hindrance decreases the rate of reaction of this position compared to that at the para position. Another factor that may favor the more rapid introduction of ^{13}C at the para position than at the meta position is the greater stabilization of the intermediate benzylic carbocation **10b**, compared to the meta-oriented cation **17b** (Scheme III). The para-oriented cation has additional stabilization by hyperconjugation with structure **16b**. The formation of the cation **10b** is critical to the dealkylation step that produces ethylbenzene-*4*-^{13}C (**13b**). Even if cation **17b** does react with **4b** to produce ethylbenzene-*3*-^{13}C (**24b**) as shown in Scheme IV, the conversion of the intermediate **20b** to **22b** will not be as facile as the corresponding conversion of **11b** to **12b** which leads to ethylbenzene-*4*-^{13}C. These conversions involve an electrophilic attack of H^+ on a diphenylethane intermediate, and this will occur less readily on the meta-oriented diphenylethane **21b** than on the corresponding para-oriented diphenylethane involved in the conversion of **11b** to **12b**.

It is interesting to note that the increase in ^{13}C content occurred at almost equal rates in the ortho and meta positions. In addition to a balance between the electronic and steric effects mentioned above, there are other possible factors that may be involved. Some ethylbenzene-*2*-^{13}C could be formed by an intermolecular mechanism that does not involve the intermediate formation of *o*-diethylbenzene. Such a mechanism is suggested in Scheme V. Ethylbenzene-*3*-^{13}C (**24b**), which has been produced by

Table II. Reaction of Ethylbenzene-1-^{13}C with Aluminum Bromide and Hydrogen Bromide in 1,2,4-Trichlorobenzene at 10 °C[a]

time	% eth[b]	% dieth[c]	% trieth[d]	^{13}C distribution in ethylbenzene[e] C_1	$C_{2,6}$ (ortho)	$C_{3,5}$ (meta)	C_4 (para)
0	100	0	0	0.80	0.09	0.07	0.04
30 s	98	2	0	0.81	0.09	0.06	0.04
1 min	94	6	0	0.82	0.09	0.05	0.04
2 min	92	8	0	0.80	0.09	0.06	0.05
4 min	90	10	0	0.80	0.09	0.06	0.05
6 min	89	11	0	0.81	0.09	0.06	0.04
10 min	86	13	1	0.79	0.09	0.07	0.05
15 min	82	17	1	0.81	0.08	0.05	0.06
25 min	81	18	1	0.77	0.10	0.06	0.07
40 min	79	20	1	0.79	0.09	0.06	0.06
60	75	24	1	0.76	0.10	0.07	0.07
90 min	73	26	1	0.73	0.10	0.06	0.11
2 h	72	27	1	0.71	0.09	0.08	0.12
3 h	70	29	1	0.63	0.10	0.09	0.18
5 h	68	30	2	0.53	0.11	0.11	0.25
10 h	69	29	2	0.42	0.16	0.14	0.28
20 h	69	28	3	0.35	0.16	0.18	0.31

[a] Molar ratio of ethylene/aluminum bromide/hydrogen bromide was 20:1:1, and that of ethylbenzene/1,2,4-trichlorobenzene was 1:2 (v/v). [b] Percentage of ethylbenzene. [c] Percentage of diethylbenzenes. Although benzene was produced in all experiments in which diethylbenzenes were detected, its percentage is not included in the table. [d] Percentage of triethylbenzenes. [e] The percent of ^{13}C in each position of the ring divided by total percent of ^{13}C in the ring.

Table III. Reaction of Ethylbenzene-1-^{13}C and Ethylbenzene-8-^{2}H in 1,2,4-Trichlorobenzene Catalyzed by Aluminum Bromide and Hydrogen Bromide at 10 °C[a,b]

time	% eth[c]	% dieth[d] meta	% dieth[d] para + ortho	% trieth[c]	^{13}C distribution in ethylbenzene[f] C_1	$C_{2,6}$ (ortho)	$C_{3,5}$ (meta)	C_4 (para)	% doub[g]
0	100	0	0	0	0.76	0.12	0.08	0.04	0
30 s	99	trace	1	0	0.75	0.12	0.08	0.05	0
1 min	96	2	2	0	0.78	0.11	0.07	0.04	0
2 min	93	4	2	0	0.76	0.11	0.08	0.05	0
4 min	92	5	3	0	0.76	0.11	0.08	0.05	0
6 min	92	5	3	0	0.76	0.12	0.08	0.04	0
10 min	90	6	4	trace	0.78	0.10	0.08	0.04	0
15 min	83	10	6	trace	0.72	0.13	0.08	0.07	0.29
25 min	79	12	8	trace	0.71	0.13	0.08	0.08	0.34
40 min	77	14	8	1	0.71	0.11	0.09	0.09	0.96
60 min	74	16	8	2	0.63	0.12	0.10	0.15	1.4
90 min	73	16	8	3	0.52	0.13	0.14	0.21	3.8
2 h	70	16	9	5	0.46	0.14	0.14	0.26	4.6
3 h	63	17	10	10	0.38	0.17	0.16	0.29	6.4
5 h	61	16	11	12	0.35	0.17	0.18	0.29	6.7
12	60	16	11	13	0.26	0.22	0.23	0.29	10.0
20	56	16	12	16	0.17	0.31	0.30	0.22	10.2

[a] See Experimental Section for isotopic content. [b] Molar ratio of ethylbenzene/aluminum bromide/hydrogen bromide was 10:1:1; that of ethylbenzene/1,2,4-trichlorobenzene was 1:2 (v/v). [c] Percentage of ethylbenzene. [d] Percentage of diethylbenzenes. Although benzene was produced in all experiments in which diethylbenzenes were detected, its percentage is not included in the table. [e] Percentage of triethylbenzenes. [f] Percentage of ^{13}C in each position of the ring divided by the total percentage of ^{13}C in the ethylbenzene ring. [g] Double-labeled ethylbenzene.

intermolecular transalkylation–dealkylation, undergoes nucleophilic substitution in the para position by **5b**, and subsequent dealkylations and transalkylations lead to the ethylbenzene-2-^{13}C (**29b**). Finally, the possibility cannot be excluded that *some* intramolecular isomerization accompanies the faster intermolecular transalkylations.

Further insight into the relationship between the isotopic reorientation and the transalkylation reactions of ethylbenzene-1-^{13}C was sought by means of a simultaneous reaction of ethylbenzene molecules labeled, separately, in the aromatic ring and in the side chain. For this purpose, ethylbenzene-8-^{2}H was synthesized, and a mixture of this material with ethylbenzene-1-^{13}C was treated with aluminum bromide and hydrogen bromide. The results from this experiment are presented in Table III. More efficient GC analysis of the products in this experiment allowed separation of *m*-diethylbenzene from *p*-diethylbenzene,[12] and it is interesting to note that the meta isomer predominated throughout the course of the reaction, although the isotope moved into the para position of ethylbenzene much more rapidly than into the meta position, as observed in the preceding experiment with ethylbenzene-1-^{13}C alone. Not until after 20 h did the ^{13}C content at the meta position (and the ortho position also) exceed that of the para position. This predominance of *m*-diethylbenzene over *p*-diethylbenzene does not necessarily conflict with the intermolecular transalkylation mechanism for the reorientation of ethylbenzene-1-^{13}C. As mentioned earlier, the formation of a benzylic cation such as **10b** is necessary for the dealkylation of a diethylbenzene which will result

(12) If there was any o-diethylbenzene present, it was not separated by the GC column. Judging from isomerization studies on the diethylbenzenes[7] there were probably insignificant amounts, if any.

Scheme V

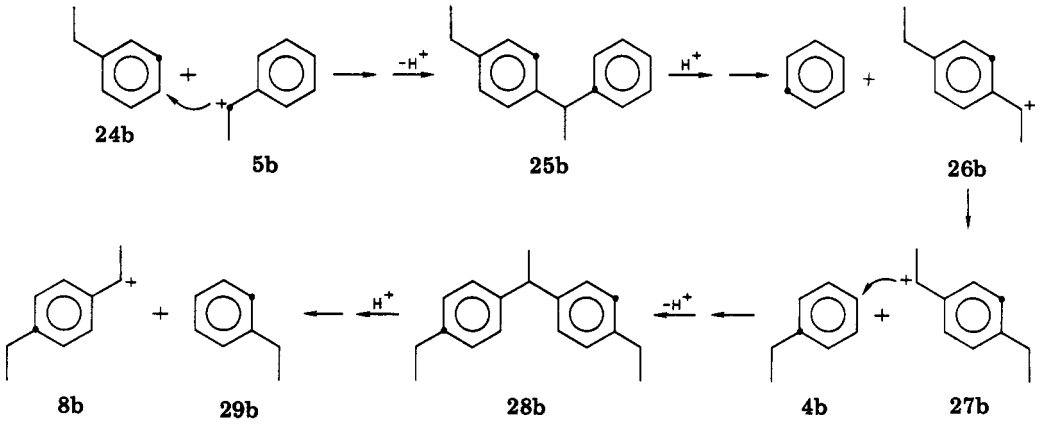


Table IV. Reaction of *n*-Propylbenzene-*1*-^{13}C with Aluminum Bromide and Hydrogen Bromide in 1,2,4-Trichlorobenzene at 10 °C[a]

		% dipr[c]			distribution of ^{13}C in the ring[e]			
time	% pr[b]	ortho + meta	para	% tripr[d]	C_1	$C_{2,6}$ (ortho)	$C_{3,5}$ (meta)	C_4 (para)
0	100	0	0	0	0.81	0.08	0.08	0.03
2 min	74	16	10	0	0.67	0.09	0.09	0.15
5 min	73	18	9	trace	0.60	0.10	0.10	0.20
10 min	72	17	8	3	0.54	0.13	0.10	0.23
15 min	70	17	8	5	0.48	0.12	0.15	0.25
25 min	70	17	8	5	0.47	0.14	0.15	0.24
40 min	68	18	7	7	0.34	0.19	0.18	0.29
60 min	64	18	8	10	0.38	0.16	0.19	0.27
90 min	64	17	7	12	0.34	0.20	0.20	0.26
2 h	64	16	7	13	0.35	0.19	0.21	0.25
3 h	63	16	7	14	0.31	0.21	0.22	0.26
5 h	61	17	7	15	0.28	0.22	0.24	0.26
10 h	60	17	8	15	0.29	0.23	0.24	0.24
24 h	59	17	8	16	0.21	0.26	0.33	0.20
48 h	59	17	7	17	0.19	0.30	0.32	0.19
72 h	58	18	8	16	0.19	0.30	0.32	0.19

[a] Molar ratio of *n*-propylbenzene/aluminum bromide/hydrogen bromide was 20:2:3; that of *n*-propylbenzene/1,2,4-trichlorobenzene was 1:2 (v/v). [b] Percentage of *n*-propylbenzene. [c] Percentage of di-*n*-propylbenzene. Although benzene was produced in all experiments in which dipropylbenzenes were detected, its percentage is not included in the table. [d] Percentage of tri-*n*-propylbenzene. [e] Percentage of ^{13}C in each position of the ring divided by the total percentage of ^{13}C in the propylbenzene ring.

in the isotopically reoriented ethylbenzene, and although more *m*-diethylbenzene than *p*-diethylbenzene may be formed,[13] the latter undergoes dealkylation more rapidly, the formation of the benzylic cation being the rate-determining step.

The increase in the ^{13}C content in the para position of the ethylbenzene molecule and the appearance of double-labeled molecules (as detected by the *m/e* M + 2 ions in the mass spectrum) occurred at almost precisely the same time, 15 min after the initiation of the reactions when about 6% of *p*-diethylbenzene had been generated. As reaction proceeded, the *m/e* M + 2 ions indicated that the expected theoretical amount of double-labeled ethylbenzene (10.3%) was produced at approximately the same time (20 h) that the equilibrium distribution of ^{13}C was detected in the ring. This result confirmed the intermolecular transalkylation–dealkylation mechanism as the major process leading to the reorientation of ^{13}C in the ethylbenzene ring, since, if an intramolecular 1,2-shift of the ethyl group took place to an appreciable extent, the ^{13}C distribution in the ring would reach equilibrium before the maximum percentage of double-labeled ethylbenzene was formed.

n-Propylbenzene. *n*-Propylbenzene-*1*-^{13}C (**4c**) was treated with aluminum bromide and hydrogen bromide in 1,2,4-trichlorobenzene solution at 10 °C, and the reaction was monitored in the same way as that of ethylbenzene-*1*-^{13}C. The results are presented in Table IV. Formation of di-*n*-propylbenzenes was observed even more rapidly than in the case of ethylbenzene; the ratio of meta to para isomers was about 2:1 throughout the course of the reaction. Tripropylbenzenes were produced more slowly, and the amount increased until a constant concentration (about 15%) was reached. The order of increase in ^{13}C content at each position in the ring of *n*-propylbenzene was similar to that in the experiments on ethylbenzene-*1*-^{13}C, indicating that the mechanism of reorientation of the isotopic carbon is the same in ethylbenzene and *n*-propylbenzene, predominantly an intermolecular transalkylation–dealkylation process, in marked contrast to the intramolecular 1,2-shift of a methyl group in toluene.

Work is in progress on similar studies of reorientation and transalkylation reactions of ^{13}C-labeled isopropylbenzene and *tert*-butylbenzene.

Experimental Section

A Varian Aerograph 2440 and Wilkens A-700 Autoprep instrument were used for analysis, separation, and purification, with

(13) The statistical ratio of two meta to one para position must be kept in mind, so that a ratio of *m/p* = 2 corresponds to an equal rate of substitution at meta and para positions. Although para substitution would be expected to be favored electronically over meta substitution, the benzylic cation (**5b**) is so reactive that is is not very selective.

variations in the lengths of columns, types of solid supports and liquid phases, and the temperatures. The other necessary details of the experiments are given in the sections to which they apply. All of the percentage compositions reported were calculated from the peak areas, which were obtained by multiplying heights by the width at half-height. The peak areas were corrected by factors determined by analysis of samples of authentic compounds.

The ^{1}H NMR spectra were obtained on a Perkin-Elmer R-12, a Varian A-60, or a Varian HA-100 instrument. The qualitative and quantitative analyses of ^{13}C-labeled compounds were determined by ^{13}C NMR analysis in $CDCl_3$ solution with a Bruker WH-90 instrument.[14] The chemical shifts are expressed in parts per million with respect to tetramethylsilane as an internal reference.

Qualitative mass spectra were obtained on a Consolidated Electrodynamic Model 21-102 mass spectrometer, modified with a high-temperature inlet system. All quantitative analyses were determined by GC/MS with a Finnigan 4023 Quadrupole mass spectrometer with an INCOS data system. The specific mass spectrometer calculations will be described in a later section.

The qualitative infrared analyses were made on a Beckman spectrophotometer, Model IR-5A. The instrument was equipped with sodium chloride optics. The liquid samples were observed in a thickness-adjustable liquid cell and the solid samples were determined in the form of Nujol mulls.

Synthesis of Alkylbenzenes-*1-^{13}C*. Barium carbonate-^{13}*C* (obtained from Monsanto Chemical Co., Mound Laboratory, AEC, and containing 92.2 mol % ^{13}C and 7.8 mol % ^{12}C) was used for the carbonation of methyl, ethyl, and *n*-propyl Grignard reagents by standard procedures.[15] The corresponding carboxylic acids were neutralized, and the sodium salts (**1a–c**) were dried and converted to their ethyl esters (**2a–c**) by reaction with ethyl phosphate.[16] Reaction of the esters with the Grignard reagent from 1,5-dibromopentane was carried out by a modification of a literature procedure.[17] Yields of the 1-alkylcyclohexanols (**3a–c**) were improved by carrying out the reactions at high dilution, as follows. The Grignard reagent from 1,5-dibromopentane, which was only slightly soluble in diethyl ether and separated as an oil, was placed in a separatory funnel and added dropwise to a large volume of diethyl ether while the ester (**2a–c**) was added dropwise simultaneously from a second separatory funnel. The dehydration and dehydrogenation step (**3** → **4**) was carried out as described,[18] with yields of 60–70%. A modified procedure was developed in which the oven of a Varian Model 600-D gas chromatograph was used to heat a 1.8 m × 9.5 mm aluminum tube filled with the platinum-on-alumina catalyst, and the 1-alkylcyclohexanol was injected repeatedly with a 50-mL syringe. Although improved yields of alkylbenzenes were obtained, some isotopic rearrangement occurred, whereas no such rearrangement occurred in the all-glass apparatus.[19] The alkylbenzenes-*1-^{13}C* were purified by preparative gas chromatography and dried over sodium hydride before use.

Synthesis of Ethylbenzene-*8-^{2}H*. Phenylethyl chloride (12 g, 85 mmol) was converted to the Grignard reagent in the usual way, and excess deuterium oxide (99.7% ^{2}H) was added dropwise with stirring. After the normal workup, the ethylbenzene-*8-^{2}H* was collected by distillation: 7 g (78%); bp 134–136 °C. Mass spectrometric analysis showed that this compound contained 86.4% of the ^{2}H label. The ^{13}C NMR spectrum was as expected.

Synthesis of Alkylbenzenes-*o-^{2}H* (Alkylbenzenes-*2-^{2}H*) for Use as Standards in ^{13}C NMR Analysis. Toluene-*o-^{2}H* and ethylbenzene-*o-^{2}H* were synthesized from *o*-bromotoluene and *o*-bromoethylbenzene by treatment with magnesium in anhydrous diethyl ether and subsequent decomposition of the Grignard products with deuterium oxide. *n*-Propylbenzene-*o-^{2}H* was prepared by oxidizing a mixture of toluene-*o-^{2}H* and ethylbenzene-*o-^{2}H* with basic permanganate to benzoic-*o-^{2}H* acid, which was converted to the methyl ester with diazomethane. Methyl benzoate-*o-^{2}H* was treated with ethylmagnesium bromide to give phenyl-*o-^{2}H*-propanone, which was then hydrogenated (Pd/C in acetic acid plus perchloric acid) to *n*-propylbenzene-*o-^{2}H*.

The ^{13}C NMR spectra of the authentic toluene-*o-^{2}H*, ethylbenzene-*o-^{2}H*, and *n*-propylbenzene-*o-^{2}H* confirmed the reported[20] assignments of ^{13}C NMR chemical shifts, which are surprising in that the order of ortho, meta, and para shifts in toluene are different from the order in ethylbenzene and *n*-propylbenzene.

^{13}C NMR Analysis of Labeled Molecules. The procedure for calculation of the enrichment of ^{13}C in the various aromatic ring positions of the alkylbenzenes before and after reaction will be illustrated by using samples of labeled and unlabeled toluene as an example.[21] The peak areas were as shown in line 1 and 2. In order to compare the two spectra, the peak areas of the

	C_1	C_o	C_m	C_p	C_{CH_3}	
unlabeled toluene	392	2535	2387	873	498	(1)
labeled toluene	4233	1547	1597	763	328	(2)

ring carbon atoms in both spectra were normalized by dividing them by the area of the side chain methyl in each sample,[22] providing the numbers shown in lines 3 and 4. The numbers

unlabeled toluene	0.78	5.09	4.79	1.75	(3)
labeled toluene	12.91	4.72	4.87	2.33	(4)

in line 4 were divided by the numbers in line 3, and the resultant values were multiplied by 1.08 (natural abundance factor of ^{13}C) and by the number of carbon atoms at each position of the aromatic ring, giving the following values for the relative enrichment

$$C_1 = 12.91/0.78 \times 1.08 \times 1 = 17.88$$

$$C_o = 4.72/5.09 \times 1.08 \times 2 = 2.00$$

$$C_m = 4.87/4.79 \times 1.08 \times 2 = 2.20$$

$$C_p = 2.33/1.79 \times 1.08 \times 1 = 1.44$$

at the various ring positions of the labeled toluene. The percentage distribution of ^{13}C in the aromatic ring of the labeled toluene was then calculated as follows:

$$17.88 + 2.00 + 2.20 + 1.44 = 23.52$$

$$C_1 = (17.88/23.52)100 = 76\%$$

$$C_o = (2.00/23.52)100 = 9\%$$

$$C_m = (2.20/23.52)100 = 9\%$$

$$C_p = (1.44/23.52)/100 = 6\%$$

It was found that the calculations of ^{13}C enrichment were more accurate when the spectra of the unlabeled standard and the labeled compound were taken of samples of similar concentration and the spectra were recorded by using the same number of scans. An instrumental phasing problem which decreased the accuracy of the calculations was reduced to an acceptable level (ca. ± 5%) by the addition of chromium acetylacetonate to the samples before each ^{13}C NMR analysis.

Toluene-*1-^{13}C*. Aluminum bromide (5.05 g, 9.5 mmol) was distilled into a 10-mL two-necked flask containing a Teflon-covered magnetic stirring bar and fitted with a rubber septum on one neck and, through the other neck, a capillary tube extending to the bottom of the flask and having a stopcock at the upper end. Argon was passed into the flask through a syringe needle inserted through the rubber septum. Toluene enriched with ^{13}C in the 1-position (4.3 g, 46.7 mmol) was added by syringe injection through the rubber septum. The reaction flask was

(14) This instrument was provided by NSF Grant No. GP-41570.
(15) Roberts, R. M.; Douglass, J. E. *J. Org. Chem.* **1963**, *28*, 1225–1229.
(16) Ropp, G. A. *J. Am. Chem. Soc.* **1950**, *72*, 2297–2299.
(17) Fields, M.; Leaffer, M. A.; Rohan, J. *Science* **1949**, *109*, 35; Fields, M.; Leaffer, M. A.; Rothchild, S.; Rohan, J. *J. Am. Chem. Soc.* **1952**, *74*, 5498–5499.
(18) Steinberg, H.; Sixma, F. L. J. *Recl. Trav. Chim. Pays-Bas* **1960**, *79*, 679–687.
(19) The isotopic rearrangement apparently occurred before aromatization of the alkylcyclohexanols. An experiment in which toluene-*1-^{13}C* was heated with aluminum powder in a sealed glass tube at 400 °C for 2 h gave no rearrangement of the isotope.
(20) "Nuclear Magnetic Resonance Spectra"; Sadtler Research Laboratories: Philadelphia, PA, 1980; spectra No. 91C (toluene), 1621C (ethylbenzene), and 8065 (*n*-propylbenzene).
(21) We thank Dr. Ben Shoulders for able assistance in this analysis.
(22) In the case of ethylbenzene and *n*-propylbenzene, the average area of a side-chain carbon was used for the normalization.

cooled in an ice–water bath, stirring was initiated, and dry hydrogen bromide was passed into the mixture through the capillary tube, the excess gas passing out through the syringe needle previously used as the inlet for argon. When the reaction mixture became a homogeneous solution, the addition of hydrogen bromide was stopped, and the ice–water bath was removed and replaced by an oil bath adjusted and kept at 35 ± 1 °C. This moment was taken as the zero reaction time. At appropriate time intervals, 0.2-mL samples of the reaction mixture were withdrawn by syringe through the rubber septum. The aliquot samples were quenched with ice–water and extracted with ether, and the ether extracts were washed with water, dried ($CaSO_4$), and analyzed by GC using a 15.3 m × 3.2 mm column containing 10% SE-30 on Chromosorb P. Toluene was isolated from the samples by means of the preparative GC instrument using a 3.1 m × 9.5 mm column containing 30% SE-30 on Chromosorb P. Quantitative ^{13}C NMR analysis was done in $CDCl_3$ solution, with 10 mg of chromium acetylacetonate (CrAcAc) added to each sample. The results are presented in Table I.

Experiments were also carried out with toluene-*1-*^{13}C (4.38 g), Al_2Br_6 (5.1 g), and HBr in 1,2,4-trichlorobenzene (10 mL) solution at 35 and at 50 °C in the same equipment used for the ethylbenzene-*1-*^{13}C and *n*-propylbenzene-*1-*^{13}C experiments (vide infra).

Ethylbenzene-*1-*^{13}C. The experiments were carried out by using one 25-mL round-bottom three-necked flask (A) in which the ethylbenzene-*1-*^{13}C and solvent was placed and a second two-necked conical flask (B) in which the aluminum bromide–hydrogen bromide reagent was prepared. The flasks were connected through rubber stoppers by a glass tube that reached from the bottom of flask B to the top of flask A; this tube had a stopcock in the center between the two flasks. Flask A was equipped with a Teflon-covered stirring bar, and the two outer necks were stoppered with rubber septums, one being used for introduction of nitrogen through a syringe needle and the other for withdrawal of aliquot samples with a syringe. In flask A was placed 4.33 g (40.8 mmol) of ethylbenzene-*1-*^{13}C and 4 mL of 1,2,4-trichlorobenzene, and the solution was cooled to 10 °C. Freshly distilled aluminum bromide (1.11 g, 2.08 mmol) was placed in flask B, 6 mL of 1,2,4-trichlorobenzene was added, the air was displaced with nitrogen, the mixture was cooled to 10 °C, and dry hydrogen bromide (0.17 g, 2.10 mmol) was passed into the mixture until a homogeneous solution was produced. The catalyst solution in flask B was then transferred to flask A by squeezing a rubber bulb which was attached to the second neck of flask B, with the stopcock open and a syringe needle serving as a vent to flask A. The stopcock was then closed, and the reaction mixture in flask A was stirred under nitrogen and kept at 35 ± 1 °C. Samples (0.5 mL) were withdrawn by a syringe at various time intervals. The samples were quenched with ice–water and extracted with ether, the ether extracts were washed with water and dried ($CaSO_4$), and the percentages of ethylbenzene, diethylbenzene, and triethylbenzene were determined by GC with the Varian 2440 instrument with a 1.8 m × 3.2 mm column containing 1.5% OV-101 on Chromosorb P. The isolation of ethylbenzene from each sample was accomplished by preparative GC on the Wilkins A-700 instrument equipped with a 3.7 m × 9.5 mm column containing 5% Bentone on Chromosorb P. The distribution of ^{13}C in the ethylbenzene ring was determined by quantitative ^{13}C NMR. The results are presented in Table II.

Ethylbenzene-*1-*^{13}C and Ethylbenzene-*8-*^{2}H. The procedure for this experiment was identical with that of the preceding experiment except that the substrate was a mixture of 2.17 g (20.5 mmol) of ethylbenzene-*1-*^{13}C and 2.16 g (20.4 mmol) of ethylbenzene-*8-*^{2}H. The isotopic analysis of this mixture, as described in an accompanying section, showed that it contained 24% ethylbenzene molecules singly labeled with ^{13}C in the 1-position and 43% ethylbenzene molecule singly labeled with ^{2}H in the 8-position (side-chain methyl group). 1,2,4-Trichlorobenzene (10 mL) was used as the solvent, and 2.22 g (4.16 mmol) of aluminum bromide and 0.33 g (4.07 mmol) of hydrogen bromide were employed in the reaction, which was carried out at 10 ± 1 °C. The aliquot samples withdrawn at various time intervals were 0.8 mL. The GC analysis of ethylbenzene, diethylbenzene, and triethylbenzene was done by using a 15.3 m × 3.2 mm column containing 10% SE-30 on Chromosorb P. Isolation of ethylbenzene from each sample was accomplished by using the preparative GC instrument with a 2.1 m × 9.5 mm column containing 10% Ucon on Chromosorb P. The distribution of ^{13}C in the ethylbenzene ring was determined as before by ^{13}C NMR analysis. The percentage of molecules labeled with both ^{13}C and ^{2}H in each sample was determined by GC/MS, and the calculations were made by the method of Biemann[23] as described in an accompanying section. The results are presented in Table III.

***n*-Propylbenzene-*1-*^{13}C.** Freshly distilled aluminum bromide (1.9 g, 3.5 mmol) and 1,2,4-trichlorobenzene (10 mL) were placed in a 25-mL three-necked flask equipped with a Teflon-covered magnetic stirring bar and nitrogen and hydrogen bromide syringe needle inlets through rubber septums. The mixture was cooled to 10 °C, and dry hydrogen bromide (0.4 g, 4.9 mmol) was added with stirring. *n*-Propylbenzene-*1-*^{13}C (4.3 g, 36 mmol) was added by syringe. After various time intervals, aliquot samples (0.7 mL) were withdrawn by syringe, quenched, and worked up in the usual manner. The analysis of the products was done by GC with a 15.3 m × 3.2 mm column containing 10% SE-30 on Chromosorb P. The isolation of recovered *n*-propylbenzene from the samples was performed on the preparative gas chromatograph equipped with a 3.1 m × 9.5 mm column containing 30% SE-30 on Chromosorb P. The distribution of ^{13}C in the *n*-propylbenzene ring was determined by ^{13}C NMR spectrometry as before. The results are recorded in Table IV.

Calculations of the Proportions of Ethylbenzene-*1-*^{13}C, Ethylbenzene-*8-*^{2}H, and Ethylbenzene-*1-*^{13}C,*8-*^{2}H Molecules in Mixtures by Mass Spectrometry. The percentage of ethylbenzene-*1-*^{13}C molecules in a sample also containing ordinary ethylbenzene and ethylbenzene-*8-*^{2}H can be calculated by Biemann's[23] method, making use of the relative abundance of ions of *m/e* 91 ($^{12}C_7H_7^+$) and 92 ($^{12}C_6{}^{13}CH_7^+$) in the mass spectrum of a mixture of such molecules, because only the ethylbenzene-*1-*^{13}C molecules are involved in the formation of the tropylium *m/e* 92 ion; the ethylbenzene-*8-*^{2}H molecules do not contribute to this *m/e* 92 ion. A calculation of this type based on the mass spectrum of the mixture of ordinary ethylbenzene, ethylbenzene-*1-*^{13}C, and ethylbenzene-*8-*^{2}H used as starting material in the experiment gave the value 24.0% ethylbenzene-*1-*^{13}C in the mixture.

The total percentage of singly-labeled molecules can be calculated from the relative abundance of the ions *m/e* 106 ($^{12}C_8{}^{1}H_{10}$) and 107 ($^{12}C_7{}^{13}C^{1}H_{10}$ and $^{12}C_8{}^{1}H_9{}^{2}H$). A calculation based on these ions in the mass spectrum of the mixture gave the value 66.8% as the sum of the percentages of the ethylbenzene-*1-*^{13}C and the ethylbenzene-*8-*^{2}H molecules present in the mixture. The difference between 66.8% and 24.0% is 42.8%, which is the percentage of ethylbenzene-*8-*^{2}H molecules in the starting material.

Calculation of the Maximum Percentage of Doubly Labeled Ethylbenzene Molecules To Be Expected from Complete Equilibration by Intermolecular Reaction. The calculations described in the preceding section gave the following composition of the starting material used in the experiment with ethylbenzene labeled separately with ^{13}C and ^{2}H: ethylbenzene-*1-*^{13}C, 24.0%; ethylbenzene-*8-*^{2}H, 42.8%; ethylbenzene (unlabeled), 33.0%. Assuming complete equilibration of the ethyl side chain among ethylbenzene molecules by an intermolecular process, the distribution of the following four possible types of ethylbenzene molecules can be calculated on the basis of simple probability: unlabeled ethylbenzene, 0.760 × 0.572 × 100 = 43.5%; ethylbenzene-*ring-*^{13}C, 0.572 × 0.240 × 100 = 13.7%; ethylbenzene-*8-*^{2}H, 0.760 × 0.428 × 100 = 32.5%; ethylbenzene-*ring-*^{13}C,*8-*^{2}H, 0.24 × 0.428 × 100 = 10.3%. Thus the maximum percentage of M + 2 ethylbenzene (*m/e* 108) to be expected from an intermolecular reaction was 10.3%.

Registry No. **1a**, 23424-28-4; **1b**, 62601-06-3; **1c**, 62601-04-1; **2a**, 3424-59-7; **2b**, 78217-95-5; **2c**, 38765-84-3; **3a**, 50530-13-7; **3b**, 78217-96-6; **3c**, 78217-97-7; **4a**, 38442-32-9; **4b**, 78217-98-8; **4c**, 78217-99-9; toluene-*2-*^{13}C, 78218-00-5; toluene-*3-*^{13}C, 78218-01-6; toluene-*4-*^{13}C, 78218-02-7; ethylbenzene-*2-*^{13}C, 78218-03-8; ethylbenzene-*3-*^{13}C, 78218-04-9; ethylbenzene-*4-*^{13}C, 78218-05-0; propylbenzene-*2-*^{13}C, 78218-06-1; propylbenzene-*3-*^{13}C, 78218-07-2; propylbenzene-*4-*^{13}C, 78218-08-3; 1,5-dibromopentane, 111-24-0; phenylethyl chloride, 622-24-2; ethylbenzene-*8-*^{2}H, 1861-04-7.

(23) Biemann, K. "Mass Spectrometry"; McGraw-Hill: New York, 1962; pp 223–227.