

conflict with our results showing that proton transfer is facilitated along the normal lipid/water interface.^{3,21,22}

Electrical conductivity in lipid multilayered systems is supposed to be supported by proton transfer.⁸⁻¹¹ It was shown to be dependent on the hydration level of the lipids and to strongly decrease when the lipids are brought to the gel state.³⁶

When comparing the conductance results on DSPC monolayers¹⁴ with the fluorescence measurements reported in Figure 2, the drop in conductance takes place in the region of the surface pressure uptake, i.e., where the loss of proton-facilitated conduction is observed by fluorescence. Due to the higher resolution in molecular areas of our data collection with the fluorescence approach, we are able to correlate this loss of conduction with the

occurrence of the gel state. From Figure 2, we can conclude that this transition occurs with a change in packing of less than 0.06 nm². This observation was missed in the conductance experiments when the phase transition was not mentioned.¹⁴

All of these observations showing that this conductive network is no longer effective when the film is in the condensed state can be explained by a dehydration of the interface when the lipids are brought to the LC state or by a conformational change of the polar headgroup region. These changes cause a disruption of the hydrogen bond network between the interfacial water and polar headgroups. But this inhibition is specific to the gel state, and as biological membranes are always fluid, we may conclude that lipid domains at their surface are putative conduits for proton movement.

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Carbon Isotope Effect Studies of the Mechanism of the Hofmann Elimination Reaction of Para-Substituted (2-Phenylethyl-1-¹⁴C)- and (2-Phenylethyl-2-¹⁴C)trimethylammonium Bromides¹

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Abstract: Carbon-14 kinetic isotope effects (KIE) were measured for the NaOEt-promoted elimination reaction of para-substituted (2-phenylethyl)trimethylammonium bromides successively labeled at the α - and β -carbons in ethanol at 40 °C. The substantial KIE observed for labeling at both carbons ($k/\alpha k = 1.050, 1.044, 1.040, 1.032, 1.019$ and $k/\beta k = 1.040, 1.040, 1.044, 1.044, 1.042$ for p -CH₃O, H, p -Cl, p -CF₃, and p -NO₂, respectively) indicates an E2 rather than an E1 or E1cB-irrev mechanism, which has substantial E1cB character in all systems studied. Since both primary β -deuterium and nitrogen-15 leaving group isotope effects have been determined by others employing similar aromatic substituents under these same reaction conditions, this system affords the best test to date of the present theories used to predict structural changes in transition states for elimination reactions and of the successive labeling approach.

"Transition state structures for elimination reactions can be examined by looking for trends in experimental data—a trend being a quantity with a specified direction but an unspecified magnitude. Given enough data on trends, it should be possible to do the sort of curve-fitting or mapping suggested for E2 reactions, in which transition states are located qualitatively on a potential-energy surface by requiring that the predictions for the given transition state structure fit the observed trends." This quotation is taken from Winey and Thornton's paper² in which they present a revised formulation of Thornton's original technique³ for analyzing the effects of substituent changes on transition-state geometry. While this statement applies to many of the methods used to investigate E2 and other elimination reaction mechanisms, measurement of kinetic isotope effects (KIE) provides one of the best methods for studying transition-state structures and reaction-coordinate motions. The importance of the "successive labeling" technique^{4,5} for isotope-effect studies lies in the specification of which atoms are undergoing bonding changes in going from the reactants to the transition state. Elimination reactions are especially susceptible to KIE mechanistic studies using the successive labeling approach, since there are so many atoms at

which there are bonding changes in the transformation from reactants to products. In order to exploit this KIE method even further, trends in the isotope effects for each atom undergoing bonding changes should be measured as a function of systematic changes in substrate and/or reaction conditions. The present research involves such a KIE study of the NaOEt-promoted Hofmann elimination reactions of successively α - and β -carbon-14 labeled para-substituted (2-phenylethyl)trimethylammonium ions, ZC₆H₄ ^{β} CH₂ ^{α} CH₂N⁺Me₃. We have made measurements in KIE trends as the substituent, Z, at the para position of the aromatic ring in the ions is changed. Such substituent changes have the potential to alter the transition-state structure, the timing of bonding changes, and the detailed nature of the reaction coor-

(1) This research was supported by the National Science Foundation. It is taken largely from the Ph.D. dissertation of J.R.I.E., Department of Chemistry, University of Arkansas, Fayetteville, AR, 1981, to which reference should be made for further details. A preliminary report on this work appeared in a summary paper: Fry, A.; Sims, L. B.; Eubanks, J. R. I.; Hasan, T.; Kanski, R.; Pettigrew, F. A.; Crook, S. *Proc. Int. Symp. Appl. Labeled Compounds*; Duncan, W. P., Susan, A. B., Eds.; Elsevier: Amsterdam, 1983; pp 133-138.

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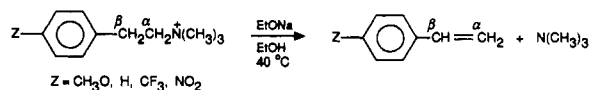
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Table I. Literature Reports of Kinetic Isotope Effects for the NaOEt-Promoted Elimination Reaction of Para-Substituted (2-Phenylethyl)trimethylammonium Ions, $ZC_6H_4^{\beta}CH_2^{\alpha}CH_2N^+Me_3$

isotopic label	KIE type	Z	T (°C)	KIE $k/^*k$	std dev	ref no.
β -D ₂	1°	H	50	2.98	0.08	6
β -D ₂	1°	CH ₃ O	40	2.64	0.04	7
β -D ₂	1°	H	40	3.23	0.04	7
β -D ₂	1°	Cl	40	3.48	0.06	7
β -D ₂	1°	CF ₃	40	4.15	0.05	7
α -D ₂	2°	H	40	1.03		11
β -T	2°	H	40	1.259	0.0102	12
β -T	2°	Cl	50	1.2821	0.030	12
β -T ^a	1°	NO ₂	22	13.5	4	14
β -T ^a	2°	NO ₂	22	1.18	0.10	14
¹⁵ N	1°	H	40	1.0117	0.0007	8
¹⁵ N	1°	H	40	1.0142	0.0004	9
¹⁵ N	1°	CH ₃ O	40	1.0137	0.0009	7
¹⁵ N	1°	H	40	1.0133	0.0002	7
¹⁵ N	1°	Cl	40	1.0114	0.0009	7
¹⁵ N	1°	CF ₃	40	1.0088	0.0006	7
β - ¹⁴ C ^b	1°	H	40	1.0448	0.0002	13
β - ¹⁴ C	1°	H	50	1.0387	0.0010	13
β - ¹⁴ C	1°	H	60	1.0313	0.0007	13
β - ¹⁴ C	1°	H	70	1.0277	0.0007	13

^a NaOMe-MeOH was used as the base system instead of NaOEt-EtOH. ^b A comparable β -carbon-14 KIE value of 1.0407 \pm 0.0011 was determined in this study (see Table III).

dinate; there might even be a change to a completely different reaction mechanism. Following previous research,⁶⁻⁹ we have studied these Hofmann elimination reactions in ethanol at 40 °C.



Choice of this reaction system for these carbon KIE studies was strongly influenced by the availability of both primary β -deuterium^{6,7} and nitrogen leaving group⁷⁻⁹ isotope effect results for similarly substituted salts, measured under the same reaction conditions. The combination of these literature results with those obtained in this research should afford the best test to date of the present theories used to predict structural changes in transition states for elimination reactions¹⁰ and of the successive labeling approach.^{4,5} The secondary α -deuterium,¹¹ secondary β -tritium,¹² and primary β -carbon-14¹³ isotope effects for $C_6H_5CH_2CH_2N^+Me_3$ and the secondary β -tritium¹² isotope effects for p -ClC₆H₄CH₂CH₂N⁺Me₃ have also been determined under these same reaction conditions. The primary and secondary β -tritium¹⁴ isotope effects for p -NO₂C₆H₄CH₂CH₂N⁺Me₃ have been determined in NaOMe-MeOH at 22 °C. All of these literature results are summarized in Table I.

Procedure and Results

The carbon-14 α - and β -labeled salts, $ZC_6H_4^{\beta}CH_2^{\alpha}CH_2N^+Me_3Br^-$, needed for the isotope-effect experiments were prepared from commercially available Na¹⁴CN and para-substituted benzoic- α -¹⁴C acids by the procedures described in the Experimental Section.

As a preliminary to the isotope-effect experiments, the kinetics

Table II. Second-Order Rate Constants for the NaOEt-Promoted Elimination Reactions of Para-Substituted (2-Phenylethyl)trimethylammonium Bromides, $ZC_6H_4CH_2CH_2N^+Me_3Br^-$, in Ethanol at 40 °C

Z	$k_2 \times 10^4$ ^a (M ⁻¹ s ⁻¹)	$k_2 \times 10^4$ ^b (M ⁻¹ s ⁻¹)	$k_2 \times 10^4$ ^c (M ⁻¹ s ⁻¹)
CH ₃ O	0.439 \pm 0.017	0.420 \pm 0.003	0.454 \pm 0.041
CH ₃	1.35 \pm 0.03		
H	4.45 \pm 0.06	4.33 \pm 0.05	4.72 \pm 0.17
Cl	29.2 \pm 0.08	29.9 \pm 0.6	29.0 \pm 0.4
CF ₃		1943 ^d \pm 6	2 \times 10 ³ (ca.) ^e
NO ₂			2 \times 10 ⁵ (ca.) ^e

^a Determined by Saunders, Bushman, and Cockerill. ^b Determined by Smith and Bourns. ^c Determined in this study. ^d Extrapolated from lower temperature reactions by Smith and Bourns. ^e Extrapolated from the Hammett equation with σ^- substituent constants and a ρ reaction constant of +3.66.

for the NaOEt-promoted Hofmann elimination reactions of the para-substituted salts were determined in anhydrous EtOH at 40 °C according to the procedures of Saunders, Bushman, and Cockerill¹⁵ and Smith and Bourns.^{7,8} The data gave linear second-order plots with no noticeable nonlinearity to greater than 90% completion. Rate constants were calculated and are summarized in Table II where they are compared to literature values. Agreement of our values and those from the literature is excellent.

Most of the isotope-effect experiments were carried out by the same procedures as those used for the kinetics measurements; details are presented in the Experimental Section. For the very fast reactions with the p -NO₂ and p -CF₃ compounds, the "limited-base" procedure^{16,17} was used (see below). For all of the KIE experiments with the p -CH₃O compound and for a few of the other experiments (see the footnotes to Table III), the product styrenes polymerized before they could be derivatized for radioactivity assay. For these cases, only one method, rather than the usual four (see below), could be used for the isotope-effect calculations.^{18,19} Except for the p -CH₃O compound, the initial salts, the product styrenes, and the salts recovered after partial reaction were all converted quantitatively to the corresponding styrene dibromides for the radioactivity measurements. For the p -CH₃O compound, because of the polymerization problem, no measurements could be made on the styrene, and for the initial and recovered salts, the radioactivities had to be determined directly from the salt. The molar activities of the various compounds were determined by liquid scintillation counting by our usual procedures.¹⁹

The carbon-14 isotope-effect values, $k/^*k$ and $k/^{\beta}k$, were calculated from the molar activities measured at each fraction of reaction (five to eight fractions ranging from approximately 20% to approximately 70% for each of the ten labeled compounds) from the equations of Tong and Yankwich.¹⁸ These equations permit the calculation of $k/^*k$ or $k/^{\beta}k$ in four ways with any combination of three of the four measured parameters: the fraction of reaction, f ; the activity of the product, R_p ; the activity of the starting salt, R_0 ; and the activity of the salt recovered after partial reaction, R_r . The KIE obtained in this research are summarized in Table III. The good agreement seen in Table III among the values calculated in the four ways just mentioned, taken together with the good agreement (lack of trends within the experimental error limits) among the results from the different fractions of reaction, gives us confidence in the chemical and radiochemical purities of the reactants and products and in the adequacy of our KIE measurement and workup procedures. For the p -NO₂ compound, only the equation using R_0 , R_r , and f gave consistent

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Table III. α -Carbon-14 and β -Carbon-14 Kinetic Isotope Effects for the NaOEt-Promoted Elimination Reactions of Para-Substituted (2-Phenylethyl)trimethylammonium Bromides, $ZC_6H_4\beta CH_2\alpha CH_2N^+Me_3Br^-$, in Ethanol at 40 °C

Z	KIE position	$^{12}k/^{14}k \pm$ SD obtained from:				av $^{12}k/^{14}k \pm$ SD (all methods)
		R_o, R_r, R_p	f, R_o, R_r	f, R_o, R_p	f, R_r, R_p	
CH ₃ O ^a	k/ α k		1.0499 \pm 0.0024			1.0499 \pm 0.0024
H ^b	k/ α k	1.0435 \pm 0.0015	1.0459 \pm 0.0017	1.0429 \pm 0.0018	1.0442 \pm 0.0014	1.0441 \pm 0.0019
Cl ^c	k/ α k	1.0402 \pm 0.0015	1.0417 \pm 0.0017	1.0396 \pm 0.0019	1.0406 \pm 0.0014	1.0405 \pm 0.0017
CF ₃ ^d	k/ α k	1.0318 \pm 0.0021	1.0298 \pm 0.0096	1.0325 \pm 0.0024	1.0312 \pm 0.0045	1.0315 \pm 0.0053
NO ₂ ^e	k/ α k	1.0192 \pm 0.0021	1.0199 \pm 0.0096	1.0188 \pm 0.0024	1.0193 \pm 0.0045	1.0192 \pm 0.0053
CH ₃ O ^f	k/ β k		1.0400 \pm 0.0017			1.0400 \pm 0.0017
H ^b	k/ β k	1.0403 \pm 0.0009	1.0393 \pm 0.0014	1.0407 \pm 0.0010	1.0401 \pm 0.0008	1.0407 \pm 0.0011
Cl ^b	k/ β k	1.0432 \pm 0.0013	1.0438 \pm 0.0046	1.0440 \pm 0.0014	1.0438 \pm 0.0017	1.0438 \pm 0.0024
CF ₃ ^b	k/ β k	1.0435 \pm 0.0032	1.0452 \pm 0.0074	1.0421 \pm 0.0018	1.0443 \pm 0.0049	1.0436 \pm 0.0045
NO ₂ ^g	k/ β k		1.0424 \pm 0.0034			1.0424 \pm 0.0034

^a From six fractions of reaction; recovered styrene (R_p) polymerized in all cases. ^b From seven fractions of reaction; recovered styrene (R_p) polymerized in one case. ^c From six fractions of reaction; in no case did the recovered styrene (R_p) polymerize. ^d From eight fractions of reaction; recovered styrene (R_p) polymerized in one case. ^e From six fractions of reaction; recovered styrene (R_p) polymerized in one case. ^f From eight fractions of reaction; recovered styrene (R_p) polymerized in all cases. ^g From six fractions of reaction.

Table IV. Fractions of Reaction, Molar Activities, and α -Carbon-14 Kinetic Isotope Effects for the NaOEt-Promoted Elimination Reaction of [2-(*p*-Chlorophenyl)ethyl]trimethylammonium-1-¹⁴C^a Bromide, *p*-ClPhCH₂ α CH₂N⁺Me₃Br⁻, in Ethanol at 40 °C

fraction of reaction (f)	$(R_r \pm$ SD) $\times 10^4$ (mCi/mol)	$(R_p \pm$ SD) $\times 10^4$ (mCi/mol)	k/ α k obtained ^b from:			
			R_o, R_r, R_p	f, R_o, R_r	f, R_o, R_p	f, R_r, R_p
0.348 ^c	5338 \pm 5	5061 \pm 5	1.0430	1.0445	1.0427	1.0433
0.406 ^c	5340 \pm 6	5076 \pm 8	1.0401	1.0420	1.0395	1.0405
0.449 ^d	5355 \pm 8	5081 \pm 7	1.0402	1.0416	1.0398	1.0406
0.493 ^d	5376 \pm 8	5093 \pm 7	1.0393	1.0424	1.0382	1.0402
0.565 ^c	5397 \pm 7	5098 \pm 7	1.0399	1.0395	1.0400	1.0397
0.715 ^d	5490 \pm 8	5133 \pm 7	1.0385	1.0404	1.0372	1.0394

^a $R_o = 5229 \pm (5 \times 10^4)$ mCi/mol. ^b Overall mean k/ α k = 1.0405 \pm 0.0017. ^c Limited-base technique, mean k/ α k = 1.0412 \pm 0.0018. ^d Normal kinetic method, mean k/ α k = 1.0398 \pm 0.0014.

Table V. Fractions of Reaction, Molar Activities, and β -Carbon-14 Kinetic Isotope Effects for the NaOEt-Promoted Elimination Reaction of [2-(*p*-Chlorophenyl)ethyl]trimethylammonium-2-¹⁴C^a Bromide, *p*-ClPh β CH₂CH₂N⁺Me₃Br⁻, in Ethanol at 40 °C

fraction of reaction (f)	$(R_r \pm$ SD) $\times 10^4$ (mCi/mol)	$(R_p \pm$ SD) $\times 10^4$ (mCi/mol)	k/ β k obtained ^b from:			
			R_o, R_r, R_p	f, R_o, R_r	f, R_o, R_p	f, R_r, R_p
0.233 ^c	1883 \pm 3	1790 \pm 3	1.0449	1.0508	1.0441	1.0456
0.303 ^d	1884 \pm 3	1793 \pm 2	1.0434	1.0384	1.0443	1.0426
0.402 ^c		1797 \pm 2			1.0451	
0.408 ^c	1900 \pm 4	1802 \pm 4	1.0419	1.0434	1.0416	1.0423
0.501 ^d	1914 \pm 3	1802 \pm 3	1.0451	1.0438	1.0436	1.0449
0.596 ^c	1924 \pm 3	1809 \pm 2	1.0430	1.0394	1.0449	1.0417
0.711 ^d	1965 \pm 3	1820 \pm 4	1.0441	1.0468	1.0423	1.0454

^a $R_o = (1859 \pm 3) \times 10^4$ mCi/mol. ^b Overall mean k/ β k = 1.0438 \pm 0.0024. ^c Limited-base technique, mean k/ β k = 1.0438 \pm 0.0028. ^d Normal kinetic method, mean k/ β k = 1.0439 \pm 0.0022.

results. It appears that some side reaction is interfering with the proper isolation and purification of the styrene derivatives; for this reason the results from the *p*-NO₂ compound may be somewhat more uncertain than those from the other compounds.

While the limited-base technique has been used by others,^{16,17} no detailed check of its validity for isotope-effect experimentation has been reported. To check this point, elimination reaction KIE experiments were carried out for both the α - and β -labeled *p*-Cl compounds by both the "normal" and the "limited-base" methods. The results from the two methods are practically identical, as shown in Tables IV and V. For the α -labeled compound, the overall KIE values are 1.0398 and 1.0412, respectively; for the β -labeled compound, the values are 1.0439 and 1.0438. This excellent agreement confirms the validity of interchanging these two techniques. For the faster reacting systems studied, the *p*-NO₂ and *p*-CF₃ compounds, use of the limited-base procedure is a must. Other measurements in this laboratory on the related 2-phenylethyl chloride system gave similar results.²⁰

Discussion

As can be seen from the results in Table III, there are substantial carbon-14 KIE at both the α - and β -carbons in the EtONa-promoted Hofmann elimination of trimethylamine from

all of the para-substituted (2-phenylethyl)trimethylammonium ions, $ZC_6H_4\beta CH_2\alpha CH_2N^+Me_3$, studied. There is a large monotonic variation in the α -carbon KIE as the substituent changes: Z, k/ α k; CH₃O, 1.050; H, 1.044; Cl, 1.041; CH₃, 1.032; NO₂, 1.019. However, there is no trend with Z, within experimental error, for the β -carbon KIE: Z, k/ β k; CH₃O, 1.040; H, 1.040; Cl, 1.044; CF₃, 1.044; NO₂, 1.042. These KIE show clearly that there are large bonding changes at both C _{α} and C _{β} in the rate-determining steps for each of the Z-substituted compounds. In the (considered unlikely anyway) E1-irrev mechanism, there would be no bonding changes at the β -carbon, so that mechanism is ruled out. In the E1cB-irrev mechanism, there could be only small secondary isotope effects at the α -carbon, so that mechanism is ruled out also. The E1cB-rev mechanism is ruled out as well by the fact that no exchange was observed⁹ between the EtOH solvent and the β,β -dideuterated substrate, $ZC_6H_4CD_2CH_2N^+Me_3$, for the Z = H and Z = CF₃ compounds when the EtONa-promoted elimination reaction was stopped after half reaction. Furthermore, this mechanism is also ruled out by the fact that large β -deuterium KIE have been observed⁷ for the Z = CH₃O, H, Cl, and CF₃ compounds. (Reversible carbanion formation would have "washed out" the β -deuteriums, thus making it impossible to measure the β -deuterium KIE.) The inescapable conclusion is that all of these reactions have an E2 mechanism, albeit with (probably, see below) considerable amounts of E1cB character, the amount varying with Z.

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Because the overall elimination reaction involves both bond rupture and bond formation at both C_α and C_β , these carbon KIE cannot be interpreted in the simple terms of "a larger KIE means more bond breaking at that carbon in the transition state",⁴ as is possible for KIE measurements at terminal atoms. For that reason, qualitative discussion of trends or lack of trends in the α - and β -carbon KIE as the substituent Z varies is not straightforward. Our research group has reported¹⁰ the results of an extensive computer-modeling carbon, nitrogen, and deuterium KIE study of this reaction, and it was possible to reproduce the experimental KIE trends of this research quite well. The modeling calculations on this and related systems are continuing, but for the present purpose, a more qualitative approach will be taken in an attempt to rationalize all of the available data into a unified description of the basic mechanism and of how it changes as the substituent changes. The monotonic trends with the substituent changes observed for the nitrogen and β -deuterium KIE are more readily interpreted because they involve (largely) either terminal nitrogen KIE ("simple bond rupture") or well-understood three-centered hydrogen-transfer deuterium KIE results (see below).

The Hofmann elimination of these $ZC_6H_4CH_2CH_2N^+Me_3$ compounds has been much studied, and a great deal is known about the mechanism of the reaction. The present and all previous data point to an E1cB-like E2 mechanism under almost all reaction conditions.²¹ The previous evidence will be summarized briefly as a prelude to our more extensive discussion of our present results. In addition to their nitrogen KIE and deuterium KIE and exchange studies, Smith and Bourns have also ruled out⁹ the less likely α -elimination and ylide elimination reaction mechanisms by using tracer experiments with α - and β -labeled substrates. Stereochemical studies by Bourns and Frosst²² have also shown that this reaction proceeds almost exclusively by anti alignment of the β -hydrogen and the leaving group in the transition state. The Hammett ρ reaction constant for this system is 3.58 ± 0.01^{15} using normal σ substituent constants and 3.66 ± 0.01^7 (3.62 ± 0.002 as determined in this laboratory) using σ^- substituent constants. These high positive ρ values are comparable to those obtained from the rates of methyl-hydrogen exchange of substituted toluenes with lithium cyclohexylamide in cyclohexylamine, which gave a ρ value of +4 at 50 °C,²³ and from the rates of the polymerization of substituted styrenes in THF by an anionic mechanism, which gave a ρ value of +5 at 25 °C.²⁴ One would conclude that the EtONa-promoted elimination reactions of (2-phenylethyl)trimethylammonium ions in ethanol proceed by very carbanion-like E2 transition states.

There are several reports^{7-9,25-27} of nitrogen KIE studies on this and closely related reaction systems. The definitive work is that of Smith and Bourns,⁷ who studied nitrogen-15 KIE as a function of Z in $ZC_6H_4CH_2CH_2^{15}N^+Me_3$: Z , $^{14}k/^{15}k$; CH_3O , 1.0137; Cl , 1.0114; and CF_3 , 1.0088. In accord with Hammond's postulate²⁸ (Thornton^{2,3} "parallel effect"), this trend toward lower KIE values as the substituent becomes more electron-withdrawing is what would be expected for a terminal-atom effect as the transition state becomes more reactant-like (less C_α -N bond rupture).²⁹

The question of whether the β -hydrogen is more or less than half-transferred to base at the transition state is best addressed by examining the trend with the substituent in the β -D₂ KIE. According to theory,³⁰⁻³² the magnitude of the deuterium KIE in a proton-transfer reaction should start low, increase to a maximum, and then decrease to a low value as the extent of proton transfer increases from 0 to 100%. For a case where the proton is transferring between two atoms of equal mass, the maximum would come at half-transfer. This kind of behavior is popularly known as "following the Westheimer curve". There have been numerous reports^{7,6,15,27,33-36} of β -deuterium KIE studies on the $ZC_6H_4CD_2CH_2N^+Me_3$ system, but the definitive work bearing on the question of the extent of C_α -N bond rupture relative to the extent of C_β -H bond rupture is that of Smith and Bourns,⁷ who studied the KIE as a function of substituent: Z , $^{14}k/^{15}k$; CH_3O , 2.64; H , 3.23; Cl , 3.48; and CF_3 , 4.16. In general, the KIE increases as the substituent becomes more electron-withdrawing. This would require the extent of C_β -H bond rupture to be increasing as Z becomes more electron-withdrawing, if the hydrogen is less than half-transferred at the transition state, and decreasing as Z becomes more electron-withdrawing, if the hydrogen is more than half-transferred. Since the nitrogen KIE decrease as Z becomes more electron-withdrawing, it is clear that the latter case holds and that the proton is more than half-transferred in this reaction. This conclusion is strongly supported by the very large positive ρ value for the reaction, which indicates a strongly carbanion-like transition state. Further corroborative evidence for this more than half-transferred conclusion is provided by Steffa and Thornton.³⁷ They report the secondary deuterium solvent isotope effect (NaOD in D₂O versus NaOH in H₂O) for $C_6H_5CH_2CH_2N^+Me_3Br^-$ at 80 °C to be 1.79, which is quite close to the theoretical maximum value of 1.88 for a completely transferred proton in a reaction and much greater than the 1.37 calculated for a half-transferred proton.

The few secondary deuterium isotope effects that have been measured for this system are summarized in Table I. All values are small. In particular, the secondary α -deuterium KIE for the unsubstituted compound is only 1.03.¹¹ The magnitude of the α -deuterium (or α -tritium) KIE should be dependent on the extent of C_α -N bond rupture in the transition state (the more bond rupture, the more freedom of motion for the C_α -H bond). This is consistent with the finding that better leaving groups (bromide, tosylate) usually give larger α -deuterium isotope effects than poorer leaving groups (NMe₃ and SME₂). Therefore, the small 1.03 value reported, as compared to the secondary α -deuterium isotope effect value of 1.09 for the EtONa-promoted elimination of 2-phenylethyl bromide in ethanol at 60 °C,³⁸ is clearly indicative of a largely intact C_α -N bond in the transition state (much E1cB character in the E2 mechanism).

Relatively few carbon kinetic isotope effects have been measured for β -elimination reactions. In very old work, Simon and Mullhofer¹⁴ have measured α - and β -carbon-14 KIE for elimination reactions of several aliphatic quaternary ammonium ions under both pyrolytic and alkoxide-promoted conditions. Hodnett and Dunn³⁹ reported the α -carbon-14 KIE for the Hofmann elimination reaction of p -NO₂-C₆H₄CH₂CH₂N⁺Me₃ at 100 °C

(21) There is some evidence that p -NO₂-C₆H₄CH₂CH₂N⁺Me₃ reacts by the E1cB-rev and/or E1cB-irrev mechanism in aqueous buffer solutions (Keefe, J. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1981**, *103*, 2457-2459; **1983**, *105*, 265-279). A carbon-14 KIE study of this question has been carried out in this laboratory and will be published in the near future. Even in this case there are very small α -carbon KIE.

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at a pH of 7 to be 1.078, while Simon and Mulhoffer reported¹⁴ a value of 1.026 for the same system. While the source of discrepancy between the two values of the two sets of workers is not known, the fact remains that all of these older papers report large values for the α -carbon KIE, and this rules out the possibility of an E1cB-irrev mechanism in all of the reaction systems studied. Banger, Jaffe, Liu, and Saunders^{16,40} measured β -carbon-13 KIE for the elimination reactions of $C_6H_5\beta CH_2CH_2N^+Me_3Br^-$ and $C_6H_5\beta CH_2CH_2S^+Me_2Br^-$ with NaOH in mixtures of Me_2SO and H_2O . Miller, Subramanian, and Saunders¹³ measured β -carbon-14 KIE as a function of temperature for the elimination reactions of $C_6H_5\beta CH_2CH_2N^+Me_3I^-$ with NaOH in mixtures of Me_2SO and H_2O and with NaOEt in EtOH. Tao, Wu, Hargreaves, and Saunders^{41,42} measured α -carbon-14 KIE for the elimination of $C_6H_5CH_2\alpha CH_2N^+Me_3Br^-$ and $C_6H_5CH_2\alpha CH_2S^+Me_2Br^-$ with NaOH also in mixtures of Me_2SO and H_2O . Although both the S^+Me_2 and N^+Me_3 reaction systems exhibited both maxima and minima in their β -carbon KIE as the ratio of Me_2SO to H_2O was increased, the trends for the N^+Me_3 reaction system were very small. The α -carbon KIE were virtually invariant. The authors have analyzed their experimental carbon KIE values by comparing them to values calculated from various transition-state models, corrected and uncorrected for tunneling. They concluded that carbon isotope effects are small or even inverse without tunnel corrections and that tunnel corrections appear to make the major contribution to the observed values. Most of the C_α and C_β isotope effects reported here, using a different reaction medium, are much larger than those reported by Saunders' group; it seems unlikely that tunneling could account for the major portion of our values. Our calculations paper¹⁰ speaks to this point to some extent. The only reported carbon isotope effects for the β -elimination reactions that involve a halide ion as the leaving group are those by Kanski, Fry, and Crook¹ for the 1,1,1-trichloro-2,2-diphenylethane system; Pulay and Fry⁴³ for the 1,1-dichloro-2,2-diarylethane system; Hasan, Sims, and Fry¹⁹ for the 1-phenylethyl chloride system; and Pettigrew²⁰ for the 2-phenylethyl chloride system. The trends in the carbon isotope effects were determined at both the α - and β -carbons as the aryl substituent was varied. Because substantial isotope effects were observed for both carbons in every case, it was concluded that all of these reactions proceed by the E2 mechanism, with transition states having varying degrees of E1cB and E1 character.¹ The only reported KIE for a syn elimination reaction are those of Wright, Sims, and Fry for the thermal decomposition of (2-phenylethyl)dimethylamine oxides.⁴⁴

It is convenient to discuss our results and those from the literature in terms of an elimination reaction transition-state diagram, first utilized in our 1972 review paper.⁴ For this $ZC_6H_4\alpha CH_2\beta CH_2N^+Me_3$ system, these diagrams plot the bond order for the $C_\alpha-N$ bond order vs the bond order for the $C_\beta-H$ bond. Such plots can be thought of as plane projections onto a flat surface of the infinite variety of E2 potential surfaces so ably presented by More O'Ferrall.⁴⁵ Each point within the diagram represents a particular transition state for an E2 mechanism, with more or less E1 or E1cB character and more or less reactant-like or product-like character. Each point should be thought of as representing a complete (imagined) More O'Ferrall potential surface. The mechanistic diagram is bounded at the left ordinate by the E1-irrev mechanism and at the bottom abscissa by the E1cB-irrev mechanism. These plots have been used in a most effective way by Winey and Thornton² in delineating the effects of various reaction parameters on transition-state placement (within the E2 spectrum) and structure. Such charts are now in extensive use in the isotope-effect field.^{1,32,46,47} Figure 1 is such

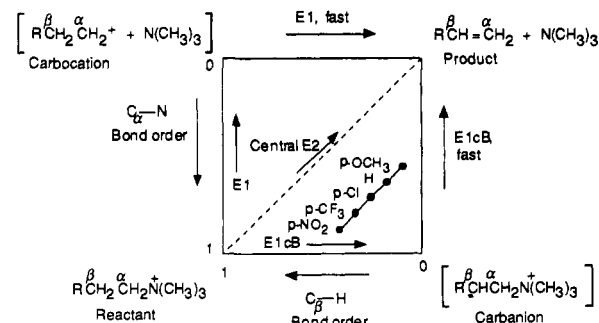


Figure 1. E2 mechanistic spectrum and transition-state trend diagram for the NaOEt-EtOH-promoted elimination reaction of para-substituted (2-phenylethyl)trimethylammonium ions.

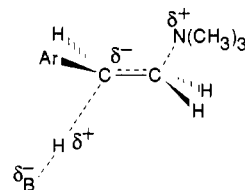


Figure 2. E1cB-like E2 antiperiplanar transition-state structure for the Hofmann elimination reaction of the (2-phenylethyl)trimethylammonium ion system.

a plot containing our evaluation of the mechanism of the Hofmann elimination reactions of the compounds used in this research.

From the evidence presented above, it is clear that the general mechanism of these Hofmann elimination reactions is of the E1cB-like E2 type, that the β -proton is more than half-transferred to base at the transition state, and that the transition state becomes more reactant-like and more E1cB-like as the substituent, Z, becomes more electron-withdrawing. These conclusions have dictated the placement of the trend-with-substituent line in Figure 1. These reactions are all in the E1cB-like E2 section of the diagram, and it should be noted that there must be strong horizontal components to the reaction-coordinate motions at the transition states. These conclusions are in full agreement with those of Smith and Bourns,⁷ who propose that 2-phenylethyl substrates with good leaving groups such as bromide ion react by a near-central E2 transition state, with reaction-coordinate motion that involves both extensive proton transfer and leaving group departure. Following the lead of Smith and Bourns⁷ and using the detailed approaches of Winey and Thornton² and McLennan,⁴⁸ replacing the good leaving group, bromide, with the poorer leaving group, NMe_3 , will perturb the (More O'Ferrall-type⁴⁵) potential surface to shift the mechanism toward the E1cB (lower right) corner of the diagram. It is convenient to think of such a change that stabilizes the carbanion as "pulling down" the lower right corner of the potential surface, which distorts the entire surface, shifting the position of the transition state in the E1cB-like direction (perpendicular effect) and also in the reactant-like direction (parallel effect, Hammond postulate effect). The more electron-withdrawing Z becomes, the greater the stabilization of the carbanion, the greater the distortion of the potential surface, and the greater the shift of the mechanism toward the E1cB axis and the reactant. This leads directly to the placement of the trend-with-substituent line in Figure 1. We have generated a similar diagram, with a similar trend-with-substituent line, by the theoretical calculations of KIE for a series of transition-state models within the E1cB-like region of the E2 mechanistic spectrum.¹⁰

The nitrogen and β -deuterium KIE data⁷ are in full accord with the above interpretation if, and only if, the proton is more than half-transferred to base for all of the Z-substituted compounds.

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It remains to examine the carbon KIE results of the present research to see if they are consistent with the placement of the transition state and transition-state trend-with-substituent line within the E1cB-like E2 mechanistic quadrant of the diagram. Several bonds involving carbon are altered in going from reactants to the transition state in β -elimination reactions. Generally speaking, a decrease in the total amount of bonding to carbon in the transition state will increase the magnitude of the observed isotope effect, and an increase in the total bonding will decrease it.

If we examine the bonding changes at C_α in the transition state for an E1cB-like E2 mechanism (Figure 2) in terms of the predicted magnitude of the α -carbon isotope effect, we would expect an increase in the α -carbon isotope-effect value as the extent of C_α -N bond rupture is increased, and a decrease in the α -carbon isotope-effect value as the extent of C_β - C_α double bond formation is increased. Similarly, an increase in the extent of proton transfer at C_β should increase the β -carbon isotope-effect value, while an increase in the extent of C_β - C_α double bond formation and/or an increase in the bonding of C_β to the aromatic ring by means of delocalization of negative charge into the ring should decrease the β -carbon isotope effect. The magnitude of this latter effect would be expected to vary as Z varies.

The trend of $k/\alpha k$ is to lower values as Z becomes more electron-withdrawing: 1.050 for Z = CH₃O to 1.019 for Z = NO₂ (see Table III). From the trend-with-substituent line in Figure 1, we find that as a stronger electron-withdrawing group is employed, the extent of both C_β - C_α double bond formation and C_α -N bond rupture decreases. Since a decrease in double bond character should increase the α -carbon isotope effect and a shortening of the C_α -N should decrease it, the observed decrease in the α -carbon isotope effect must mean that the effect of changing the amount of double bond character on the magnitude of the α -carbon isotope effect is small. The dominating factor that appears to control the magnitude of the α -carbon isotope effect is then the extent of C_α -N bond rupture in the transition state.

No variation in the β -carbon isotope effect as a function of the para-substituent was observed within experimental error (all $k/\beta k = 1.042 \pm 0.002$; see Table III). However, a significant decrease was found for this system in the primary β -deuterium isotope effects⁷ as the electron-withdrawing ability of the aryl substituent was increased, indicative of a substantial change in the extent of C_β -H bond rupture. If we again examine the E2 mechanistic diagram in Figure 1, we find that an increase in the electron-withdrawing ability of the aryl substituent not only decreases the amount of double bond character but also decreases the extent of C_β -H bond rupture. Of course as stated before, a decrease in the C_β - C_α double bond formation should increase the β -carbon isotope effect, while a decrease in C_β -H bond rupture should decrease it. Thus, the observed β -carbon KIE must result from a combination of compensating factors, which appear to leave the net KIE the same for all Z-substituted compounds studied. This is not a result that would have been predicted, but it is at least understandable.

The completion of this study makes the EtONa-promoted Hofmann elimination reaction in the ZC₆H₄CH₂CH₂N⁺Me₃ system the best example to date of the use of the kinetic isotope effect techniques, especially the successive labeling and the variation of isotope effect with substituent approaches, to elucidate transition-state structures and reaction-coordinate motions and in more general terms to determine reaction mechanisms.^{1,4,5,49,50} The qualitative analysis presented here and the more quantitative matching of experimental and calculated KIE results we have reported earlier¹⁰ complement each other very well and together represent one of the best methods, perhaps the very best method,

available for obtaining the intimate details of transition-state structure, timing of binding changes, and reaction-coordinate motions.

Experimental Section

General Remarks. All melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. ¹H NMR spectra were measured on a Varian Model EM-360 spectrometer. IR spectra were recorded on a Perkin-Elmer Model 283 grating IR spectrophotometer, and UV extinction coefficients (ϵ) and absorbances were determined on a Gilford Model 252 updated Beckman DU spectrophotometer. The radioactivity determinations were performed on a Beckman Model CPM-100 liquid scintillation counter with the external standard ratio method.¹⁹ Details of the procedures used are given later in this section.

Materials. Ethanol was dried over a mixture of sodium (7 g/L) and diethyl phthalate (27.5 g/L) and distilled as needed through a 24-in. Vigreux column under nitrogen.⁵¹ Diethyl ether and tetrahydrofuran (THF) were dried by distillation from sodium and benzophenone. Standard EtONa-EtOH solutions were prepared from freshly cut sodium (ca. 25 g), which had been melted under xylene (200 mL); this xylene was discarded, and the sodium was washed with xylene (100 mL) and then with EtOH (200 mL). The EtONa-EtOH solution was standardized by titration against previously standardized hydrochloric acid with bromothymol blue as the indicator.

Preparation of Labeled Compounds. Each step of the synthetic sequences used for labeled compounds was carried out with unlabeled material first to maximize yields. Vacuum distillation and recrystallization were the usual methods of purification. Vacuum distillation of the labeled compound was followed by two chaser distillations with the unlabeled compound to maximize the yield. The structures of labeled compounds were verified by comparison of ¹H NMR spectra, boiling points, and melting points to those previously reported and obtained for the corresponding unlabeled compound.

Benzyl- α -¹⁴C alcohol was prepared by reduction of benzoic- α -¹⁴C acid with lithium aluminum hydride (LAH).⁵² A solution of commercial benzoic- α -¹⁴C acid (0.33 mol) in diethyl ether (200 mL) was added dropwise with stirring to a mixture of LAH (0.37 mol) and diethyl ether (75 mL) at gentle reflux. After 24 h at reflux, the intermediate complex was decomposed by carefully adding water (14 mL), aqueous sodium hydroxide (15%, 14 mL), and water (42 mL), respectively.⁵³ The inorganic white precipitate was removed by filtration, and the ethereal solution was dried (MgSO₄) and concentrated. The residue was vacuum distilled to give an 89% yield of product, bp 74 °C (2.4 mm) [lit.⁵⁴ bp 93 °C (10 mm)].

p-Methoxybenzyl- α -¹⁴C alcohol was prepared from commercial p-methoxybenzoic- α -¹⁴C acid by the procedure described for benzyl- α -¹⁴C alcohol, except tetrahydrofuran (THF) was substituted for diethyl ether. Vacuum distillation gave a 53% yield of the desired product, bp 89-90 °C (0.5 mm) [lit.⁵⁵ bp 134-135 °C (12 mm)].

p-Chlorobenzyl- α -¹⁴C alcohol was prepared from commercial p-chlorobenzoic- α -¹⁴C acid by the procedure outlined for benzyl- α -¹⁴C alcohol, substituting tetrahydrofuran for diethyl ether. The product, mp 71-72.5 °C (lit.⁵⁶ mp 75 °C), was obtained in a yield of 89% and was used without further purification.

Copper(I) cyanide-¹⁴C was prepared by the method of Barber.⁵⁷ A solution of sodium sulfite (14 g) in 50-60 °C water (40 mL) was added to copper(II) sulfate (52 g) in 40-50 °C water (160 mL), previously acidified with hydrochloric acid to the congo red end point, followed by the addition of a solution of potassium cyanide-¹⁴C (13 g) in 50-80 °C water (40 mL). The cuprous cyanide precipitated immediately. Filtration, washing with water, washing with methanol, and vacuum drying gave a 92.3% yield of the desired product.

p-(Trifluoromethyl)benzotrile- α -¹⁴C was prepared by a modification the method of Friedman and Shichter.⁵⁸ A mixture of p-bromo(trifluoromethyl)benzene (0.20 mol) and copper(I) cyanide-¹⁴C (0.19 mol) was refluxed in dimethylformamide (35 mL) with stirring for 18 h, poured into water (500 mL), and filtered. The isolated brown solid was

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stirred in hot water (300 mL) containing sodium cyanide (100 g) and ethylenediamine (50 mL) and then extracted with methylene chloride. Evaporation of the methylene chloride gave the desired product, which was used in the next step without further purification.

***p*-(Trifluoromethyl)benzoic- α - ^{14}C acid** was prepared by hydrolyzing the *p*-(trifluoromethyl)benzotrile- α - ^{14}C prepared above in dilute aqueous sodium hydroxide (25 g in 300 mL of water) at reflux for 18 h. After the reaction was cooled to room temperature, water (200 mL) was added, the solution was made acidic with sulfuric acid, and the white precipitate formed was filtered and washed with water. Recrystallization from ethanol (1 L) gave an 89.1% yield of the desired product, mp 220.5–221.5 °C (lit.⁵⁹ mp 220–221 °C).

***p*-(Trifluoromethyl)benzyl- α - ^{14}C alcohol** was prepared by the procedure outlined for benzyl- α - ^{14}C alcohol, substituting THF for diethyl ether. Vacuum distillation gave an 89.3% yield of the desired product, bp 64–65 °C (50 mm) [lit.⁶⁰ bp 78.5–80 °C (4.0 mm)].

Benzyl- α - ^{14}C chloride was prepared by the reaction of benzyl- α - ^{14}C alcohol with hydrochloric acid in the presence of zinc chloride in a similar manner to that of Whaley and Copenhaver.⁶¹ Vacuum distillation gave an 89.3% yield of the desired product, bp 46 °C (2.1 mm) [lit.⁶² bp 64–69 °C (12 mm)].

***p*-Methoxybenzyl- α - ^{14}C chloride** was prepared by the reaction of *p*-methoxybenzyl- α - ^{14}C alcohol with hydrochloric acid according to the procedure of Rorig, Johnston, Hamilton, and Telinski.⁶³ The product was used without further purification.

***p*-Chlorobenzyl- α - ^{14}C chloride** was prepared by the reaction of *p*-chlorobenzyl- α - ^{14}C alcohol with hydrochloric acid in the presence of zinc chloride as described above. Vacuum distillation gave a 72.7% yield of the desired product, bp 58 °C (0.8 mm) [lit.⁶⁴ bp 117 °C (20 mm)].

***p*-(Trifluoromethyl)benzyl- α - ^{14}C chloride** was prepared by the reaction of *p*-(trifluoromethyl)benzyl- α - ^{14}C alcohol with triphenylphosphine and carbon tetrachloride by the method of Weiss and Snyder.⁶⁵ Vacuum distillation gave a 77.8% yield of the desired product, bp 71 °C (16 mm): ^1H NMR (CD_3) δ 7.2 (m, 4), 4.3 (s, 2).

Phenylethanitrile-2- ^{14}C was obtained in 71.3% yield from benzyl- α - ^{14}C chloride and sodium cyanide according to the procedure of Vogel,⁶⁶ bp 80 °C (2 mm) [lit.¹³ bp 79–80 °C (14 mm)].

***p*-(Methoxyphenyl)ethanenitrile-2- ^{14}C** was prepared by treatment of *p*-methoxybenzyl- α - ^{14}C chloride with sodium cyanide under phase-transfer conditions.⁶⁷ A solution of the chloride (0.156 mol) in benzene (50 mL) was added to a mixture of sodium cyanide (0.18 mol), water (10 mL), and tetra-*n*-butylammonium bromide (1.9 g) and stirred vigorously for 3 h at room temperature. Water was added (100 mL), the layers were separated, and the aqueous layer was extracted with benzene (100 mL). The benzene extract was washed with water, dried (MgSO_4), concentrated, and the residue vacuum distilled to give 87.8% yield of the desired product, bp 107 °C (1.2 mm) [lit.⁶⁸ bp 152 °C (16 mm)].

***p*-Chlorophenyl)ethanenitrile-2- ^{14}C** was obtained in 90.2% yield from *p*-chlorobenzyl- α - ^{14}C chloride and potassium cyanide by the same procedure, bp 91 °C (0.3 mm) [lit.⁶⁹ bp 265–267 °C (760 mm)].

[*p*-(Trifluoromethyl)phenyl]ethanenitrile-2- ^{14}C was obtained in 76.1% yield from *p*-(trifluoromethyl)benzyl- α - ^{14}C chloride and sodium cyanide by the same procedure, bp 70–75 °C (0.5 mm) [lit.⁹ bp 131–132 °C (20 mm)].

(2-Phenylethyl)amine-2- ^{14}C was obtained by reduction of 2-phenylethanitrile-2- ^{14}C with LAH-AlCl_3 as described by Nystrom.⁶⁹ A solution of aluminum chloride (0.12 mol) in diethyl ether (150 mL) was added rapidly to a solution of LAH (0.12 mol) in diethyl ether and stirred for 5 min. A mixture of 2-phenylethanitrile-2- ^{14}C in diethyl ether was added dropwise and the reaction stirred overnight at room temperature. Water (5 mL), dilute sulfuric acid (6 N, 170 mL), and water (120 mL)

were added sequentially. The layers were separated and the aqueous layer was washed with diethyl ether (200 mL). The aqueous layer was made basic with sodium hydroxide, cooled, and extracted with diethyl ether (400 mL). The combined ethereal extracts were washed with water, dried (K_2CO_3), concentrated, and the residue vacuum distilled to give a 62% yield of the desired product, bp 55 °C (3.3 mm) [lit.¹³ bp 197–200 °C (760 mm)].

(2-Phenylethyl)amine-1- ^{14}C was obtained in 55% yield by reduction of 2-phenylethanitrile-1- ^{14}C by the same procedure, bp 59 °C (3.3 mm) [lit.¹³ bp 197–200 °C (760 mm)].

[2-(*p*-Methoxyphenyl)ethyl]amine-2- ^{14}C was obtained in 77.5% yield by reduction of 2-(*p*-methoxyphenyl)ethanenitrile-2- ^{14}C by the same procedure, bp 89–91 °C (1.0 mm), [lit.⁷⁰ bp 138–140 °C (20 mm)].

[2-(*p*-Methoxyphenyl)ethyl]amine-1- ^{14}C was obtained in 60% yield by reduction of 2-(*p*-methoxyphenyl)ethanenitrile-1- ^{14}C by the same procedure and used in the next step without further purification.

[2-(*p*-Chlorophenyl)ethyl]amine-2- ^{14}C was obtained in 64.4% yield by reduction of 2-(*p*-chlorophenyl)ethanenitrile-2- ^{14}C by the same procedure, bp 71 °C (0.5 mm): ^1H NMR (CDCl_3) δ 6.9 (m, 4), 2.7 (m, 4), 1.0 (s, 2).

[2-(*p*-Chlorophenyl)ethyl]amine-1- ^{14}C was obtained in 88.3% yield by reduction of 2-(*p*-chlorophenyl)ethanenitrile-1- ^{14}C by the same procedure, bp 70 °C (0.80 mm). The ^1H NMR spectral data were identical with that listed for the previous compound.

[2-[*p*-(Trifluoromethyl)phenyl]ethyl]amine-2- ^{14}C was obtained in 82.7% yield by reduction of 2-[*p*-(trifluoromethyl)phenyl]ethanenitrile-2- ^{14}C by the same procedure, bp 89 °C (17 mm) [lit.⁹ bp 105–106 °C (22 mm)].

[2-[*p*-(Trifluoromethyl)phenyl]ethyl]amine-1- ^{14}C was obtained in 82.7% yield by reduction of 2-[*p*-(trifluoromethyl)phenyl]ethanenitrile-1- ^{14}C by the same procedure, bp 89–91 °C (18 mm) [lit.⁹ bp 105–106 °C (22 mm)].

[2-(*p*-Nitrophenyl)ethyl]amine-2- ^{14}C was prepared by the treatment of (2-phenylethyl)amine-2- ^{14}C with fuming nitric acid according to the procedure of Goss, Hanhart, and Ingold.⁷¹ (2-Phenylethyl)amine-2- ^{14}C (0.645 mol) was added over 3 h to fuming nitric acid (90%, 350 mL) at –10 to –5 °C. After stirring for 30 min, the reaction mixture was poured into ice water (500 g), made basic with sodium hydroxide, and extracted with ether. Reextraction of the ether with dilute hydrochloric acid, evaporation of the water, and recrystallization from ethanol (95%) gave 36.4% of the corresponding hydrochloride salt, mp 213–215 °C (lit.⁷¹ mp 209–210 °C). The free amine was generated as needed by dissolving the above hydrochloride salt in water, making the solution basic, and extracting with ether.

[2-(*p*-Nitrophenyl)ethyl]amine-1- ^{14}C was obtained in 48.5% yield by the treatment of (2-phenylethyl)amine-1- ^{14}C with fuming nitric acid according to the same procedure: ^1H NMR (CDCl_3) δ 7.83 (d, 2, J = 8 Hz), 7.12 (d, 2, J = 8 Hz), 2.85 (m, 4), 1.8 (s, 2).

***N,N*-Dimethyl-*N*-(2-phenylethyl)amine-2- ^{14}C** was obtained by reductive amination of (2-phenylethyl)amine-2- ^{14}C according to the procedure of Ickes, Wisegarver, and Alles.⁷² (2-Phenylethyl)amine-2- ^{14}C was added slowly to formic acid (90%, 10 mol) followed by the addition of formaldehyde (37%, 0.6 mol). The reaction mixture was heated carefully to and maintained at 95–100 °C for 8 h, cooled, made acidic with hydrochloric acid (4 N, 100 mL), and evaporated to dryness. The residue was dissolved in water (75 mL) and extracted with ether (200 mL). The ethereal extracts were washed with water, dried (K_2CO_3), and concentrated, and the residue was vacuum distilled to give an 80.2% yield of the desired product, bp 46 °C (0.5 mm) [lit.⁷² bp 97–98 °C (22 mm)].

***N,N*-Dimethyl-*N*-(2-phenylethyl)amine-1- ^{14}C** was obtained in 75% yield by reductive amination of (2-phenylethyl)amine-1- ^{14}C by the same procedure, bp 55 °C (2.1 mm) [lit.⁷² bp 97–98 °C (22 mm)].

***N,N*-Dimethyl-*N*-[2-(*p*-methoxyphenyl)ethyl]amine-2- ^{14}C** was obtained in 72% yield by reductive amination of [2-(*p*-methoxyphenyl)ethyl]amine-2- ^{14}C by the same procedure, bp 85–86 °C (1.0 mm) [lit.¹⁵ bp 100 °C (2.0 mm)].

***N,N*-Dimethyl-*N*-[2-(*p*-methoxyphenyl)ethyl]amine-1- ^{14}C** was obtained in 59% yield by reductive amination of [2-(*p*-methoxyphenyl)ethyl]amine-1- ^{14}C by the same procedure, bp 90–91 °C (1.0 mm) [lit.¹⁵ bp 100 °C (2.0 mm)].

***N,N*-Dimethyl-*N*-[2-(*p*-chlorophenyl)ethyl]amine-2- ^{14}C** was obtained in 84.6% yield by reductive amination of [2-(*p*-chlorophenyl)ethyl]amine-2- ^{14}C by the same procedure, bp 68 °C (0.5 mm) [lit.¹⁵ bp 104–106 °C (1.2 mm)].

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N,N-Dimethyl-*N*-[2-(*p*-chlorophenyl)ethyl]amine-1-¹⁴C was obtained in 80.6% yield by reductive amination of [2-(*p*-chlorophenyl)ethyl]amine-1-¹⁴C by the same procedure, bp 64 °C (0.4 mm) [lit.¹⁵ bp 104–106 °C (1.2 mm)].

N,N-Dimethyl-*N*-[2-(*p*-(trifluoromethyl)phenyl)ethyl]amine-2-¹⁴C was obtained in 82.7% yield by reductive amination of [2-(*p*-(trifluoromethyl)phenyl)ethyl]amine-2-¹⁴C by the same procedure, bp 89–91 °C (18 mm) [lit.⁹ bp 108–108.5 °C (23 mm)].

N,N-Dimethyl-*N*-[2-(*p*-(trifluoromethyl)phenyl)ethyl]amine-1-¹⁴C was obtained in 81.9% yield by reductive amination of [2-(*p*-(trifluoromethyl)phenyl)ethyl]amine-1-¹⁴C by the same procedure, bp 90 °C (18 mm) [lit.⁹ bp 108–108.5 °C (23 mm)].

N,N-Dimethyl-*N*-[2-(*p*-nitrophenyl)ethyl]amine-2-¹⁴C was obtained by reductive amination of [2-(*p*-nitrophenyl)ethyl]amine-2-¹⁴C by the same procedure. The product was isolated as the hydrochloride salt and recrystallized once from a minimal amount of ethanol (95%) to give an 82.7% yield, mp 176.5–178 °C. The free amine was generated as needed by the same procedure described previously for (2-(*p*-nitrophenyl)ethyl)amine-2-¹⁴C and gave the following: ¹H NMR data: (CDCl₃) δ 7.89 (d, 2, *J* = 9 Hz), 7.10 (d, 2, *J* = 9 Hz), 2.65 (m, 4), 2.2 (s, 6).

N,N-Dimethyl-*N*-[2-(*p*-nitrophenyl)ethyl]amine-1-¹⁴C was obtained in 92.2% yield by reductive amination of [2-(*p*-nitrophenyl)ethyl]amine-1-¹⁴C by the same procedure. The ¹H NMR data match those of the previous compound.

(2-Phenylethyl)trimethylammonium-2-¹⁴C bromide was obtained by treatment of *N,N*-dimethyl-*N*-(2-phenylethyl)amine-2-¹⁴C with methyl bromide according to the procedure of Saunders, Bushman, and Cockerill.¹⁵ A solution of the tertiary amine (0.11 mol) in nitromethane (125 mL) was cooled to 0 °C, and methyl bromide was added until no additional precipitation of the product occurred. After being allowed to stand overnight in a sealed container, the reaction mixture was vented, poured into ether, and filtered. Recrystallization twice from a mixture of absolute ethanol and ether gave the desired product in 92.7% yield, mp 237.5–238 °C (lit.⁶ mp 238–239 °C).

(2-Phenylethyl)trimethylammonium-1-¹⁴C bromide was obtained in 85.1% yield from *N,N*-dimethyl-*N*-(2-phenylethyl)amine-1-¹⁴C by the same procedure, mp 237–238 °C (lit.⁶ mp 238–239 °C).

[2-(*p*-Methoxyphenyl)ethyl]trimethylammonium-2-¹⁴C bromide was obtained in 95.5% yield from *N,N*-dimethyl-*N*-[2-(*p*-methoxyphenyl)ethyl]amine-2-¹⁴C by the same procedure, mp 216.5 °C (lit.¹⁵ mp 217.7–218.2 °C).

[2-(*p*-Methoxyphenyl)ethyl]trimethylammonium-1-¹⁴C bromide was obtained in 96.0% yield from *N,N*-dimethyl-*N*-[2-(*p*-methoxyphenyl)ethyl]amine-1-¹⁴C by the same procedure, mp 215.5–216.5 °C (lit.¹⁵ mp 217.7–218.2 °C).

[2-(*p*-Chlorophenyl)ethyl]trimethylammonium-2-¹⁴C bromide was obtained in 91.9% yield from *N,N*-dimethyl-*N*-[2-(*p*-chlorophenyl)ethyl]amine-2-¹⁴C by the same procedure, mp 242–243 °C (lit.¹⁵ mp 242.3–242.5 °C).

[2-(*p*-Chlorophenyl)ethyl]trimethylammonium-1-¹⁴C bromide was obtained in 97.8% yield from *N,N*-dimethyl-*N*-[2-(*p*-chlorophenyl)ethyl]amine-1-¹⁴C by the same procedure, mp 241.5–242.5 °C (lit.¹⁵ mp 242.3–242.5 °C).

[2-(*p*-(Trifluoromethyl)phenyl)ethyl]trimethylammonium-2-¹⁴C bromide was obtained in 96.4% yield from *N,N*-dimethyl-*N*-[2-(*p*-(trifluoromethyl)phenyl)ethyl]amine-2-¹⁴C by the same procedure, mp 226.5–228 °C (lit.⁹ mp 227.5–228 °C).

[2-(*p*-(Trifluoromethyl)phenyl)ethyl]trimethylammonium-1-¹⁴C bromide was obtained in 96.4% yield from *N,N*-dimethyl-*N*-[2-(*p*-(trifluoromethyl)phenyl)ethyl]amine-1-¹⁴C by the same procedure, mp 224–225 °C (lit.⁹ mp 227.5–228 °C).

[2-(*p*-Nitrophenyl)ethyl]trimethylammonium-2-¹⁴C bromide was obtained in 89.5% yield from *N,N*-dimethyl-*N*-[2-(*p*-nitrophenyl)ethyl]amine-2-¹⁴C by the same procedure, mp 222–223 °C: ¹H NMR (D₂O/acetone-*d*, 50% each by volume) δ 7.9 (d, 2, *J* = 9 Hz), 7.38 (d, 2, *J* = 9 Hz), 4.32 (m, 2), 3.45 (m, 2), 3.25 (s, 9).^{15,73}

[2-(*p*-Nitrophenyl)ethyl]trimethylammonium-2-¹⁴C bromide was obtained in 71.2% yield from *N,N*-dimethyl-*N*-[2-(*p*-nitrophenyl)ethyl]amine-2-¹⁴C by the same procedure, mp 224–225 °C. The ¹H NMR data matched those of the previous compound.

Kinetic Procedure.^{7,15} Reaction rates for the NaOEt-promoted elimination of para-substituted ZC₆H₄^βCH₂^αCH₂N⁺Me₃Br⁻ in absolute EtOH were determined at 40 °C by the procedures of Saunders, Bushman, and Cockerill¹⁵ and Smith and Bourns⁷ as described below. Most reactions were carried out under second-order conditions with the concentration of the NaOEt solution varying between 0.03 and 0.05 M. The quaternary ammonium bromide (the concentration of which was main-

tained near 0.01 M) was weighed into a 250-mL volumetric flask. Absolute EtOH (195 mL) was added and the mixture was thermally equilibrated at 40 °C. The base (50 mL of ca. 0.5 M base) was added by pipet. The volume was adjusted rapidly to 250 mL, and the contents were agitated vigorously to begin the elimination reaction. No more than 2 min was required for this process. One-milliliter aliquots were withdrawn periodically with a calibrated gas-tight syringe and diluted immediately with ethanol (95%, 625-fold). The optical densities (in absorbance) were measured at the λ max values of the corresponding styrenes, from which the para-substituted styrene concentrations were determined. Wavelengths and molar absorbances (ε) measured and used in this study agreed with reported literature values.⁷⁴

In general, 10–20 aliquots were taken over the course of the reaction, and the second-order rate constant was computed for each. The rate constant for each reaction is reported in Table II as the average of the individual rate constants for the aliquots. Because UV analysis proved to be invalid for the *p*-CH₃O system (probably due to extensive polymerization of the styrene product), the method of Steffa and Thornton³⁷ was used for this compound. Individual aliquots (25 mL) were quenched in water (25 mL). The product trimethylamine was removed by evaporation under vacuum, and the residual NaOEt was titrated with standard hydrobromic acid and bromothymol blue as the indicator.

Conventional kinetics procedures for the *p*-NO₂- and *p*-CF₃-substituted compounds were not possible under similar reaction conditions. Extrapolation by means of the Hammett equation with σ substituent constants and a reaction constant, ρ, of +3.66⁷ gave the calculated rate constants listed in Table II. Use of these values gave a half-life for the *p*-CF₃ system of approximately 40 s and a half-life for the *p*-NO₂ system of approximately 0.4 s at 40 °C under the standard experimental conditions described. For the purpose of this study, determination of rate constants at lower temperatures and concentrations was not desirable (or necessary) since carbon isotope effects determined at different temperatures and under different reaction conditions may not be directly comparable. The limited-base (or limited-reactant) technique was employed in these cases.

Carbon-14 Isotope Effect Measurement Procedures. Kinetic isotope effects for the elimination reactions of α- and β-carbon-14 labeled *p*-CH₃O, unsubstituted, *p*-Cl, *p*-CF₃, and *p*-NO₂ 2-(phenylethyl)trimethylammonium bromides were measured at 40 °C in absolute ethanol with NaOEt as the base. For the first three compounds, in general, the same procedures were used in the isotope-effect experiments as were used in the kinetics experiments; the exact fractions of reaction were determined in the same way. For the very fast reacting *p*-CF₃ and *p*-NO₂ compounds, the limited-base procedure was used. The amount of base needed to bring about the desired fraction of reaction was added; the reactions stop when the base is consumed. The fractions of reaction were verified by UV analysis. In the case of the *p*-NO₂ system, the reactant displayed an appreciable ε at the λ max of the product; consequently, the concentrations of *p*-nitrostyrene were determined at a λ of 320 nm (ε = 9.28 × 10³ M cm⁻¹).

Besides the fraction of reaction (*f*), three other values are needed for the experimental carbon-14 KIE calculations: the molar activities of the starting material (*R*₀); the recovered reactant (*R*_r); and the recovered product (*R*_p).¹⁸ Thus, for each isotope-effect experiment, it is necessary to separate the recovered reactant from the product and measure the molar activity of each. A separate experiment was carried out for each compound for each fraction of reaction. Except for the *p*-NO₂ system (see below), at the end of the time needed for the desired fraction of reaction (or after the short time needed for complete reaction when the limited-base procedure was used), the samples needed for the exact fraction of reaction measurements were removed. The main body of the reaction solution (ca. 250 mL) was poured into water (400 mL) and pentane (100 mL). The aqueous layer containing the recovered reactant and sodium bromide was separated, made acidic with hydrobromic acid to the bromocresol green end point, and evaporated to dryness. The bulk of the sodium bromide was removed by extraction of the recovered reactant into acetone (3 × 100 mL). Evaporation of the acetone and recrystallization of the residue twice from a minimal amount of ethanol-ether followed by vacuum drying (100 °C) produced the recovered reactant in relatively pure form.⁹ The combined pentane layers containing the styrene products were washed with water (3 × 100 mL), dried (MgSO₄), and concentrated. The styrenes were converted to their dibromides by treatment with excess bromine in the dark. After adding a sufficient amount of saturated sodium bisulfite to decompose the excess bromine, the pentane layer was washed with water, dried (MgSO₄), and concentrated. The residue was recrystallized from an EtOH-H₂O mixture and vacuum sublimed to give analytically pure samples of the

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para-substituted styrene 1,2-dibromides suitable for radioactivity determinations (R_p). Unfortunately, it was not possible to use this procedure with the p -CH₃O compound. Despite repeated efforts, it was not possible to prevent partial polymerization of the p -methoxystyrene, so R_p could not be determined in this case. (Such polymerization reactions are known to significantly alter the molar activities of both vinylic carbons.⁷⁵)

Except for the p -CH₃O compound, the carbon-14 contents of the initial and recovered reactants (R_0 and R_r values, respectively) were also determined as their respective styrene dibromide derivatives.⁷⁵ Samples of the initial and recovered salts were allowed to undergo 100% elimination¹⁵ under conditions identical with those used to carry out the kinetics runs, except that a reaction temperature of 70 °C was used. The styrenes formed were converted to the dibromides as before. For the p -CH₃O system, the radioactivity measurements were carried out directly on the quaternary ammonium bromides themselves.

The separation procedure described above could not be used for the p -NO₂ system because the salt undergoes further elimination when heated in an aqueous medium. Instead, for the isotope-effect experiments with this compound, the reaction mixture (200 mL) was poured into ether (400 mL) and cooled in ice water. The salt that precipitated (along with sodium bromide) was filtered, washed with ether, and dried under vac-

uum at 57 °C. This precipitate, which still contained sodium bromide, was then allowed to undergo complete elimination in a separate reaction, and the resulting p -nitrostyrene was brominated, purified, and counted in a similar manner as the other compounds (R_r values). The original filtrate, which contained ether, ethanol, and the product p -nitrostyrene, was poured into cold water and the layers were separated. After the ethereal layer was washed with water and dried (MgSO₄), the corresponding styrene dibromide was prepared, purified, and counted as described above (R_p values).

Our standard procedure^{19,76} was used for the radioactivity measurements; when the quaternary ammonium bromides were counted, 0.5 mL of methanol was added to solubilize them in the standard toluene-based cocktail-fluor solution (15 mL per sample) normally used. The isotope effects (rate-constant ratios) were calculated from the equations of Tong and Yankwich (see the Procedure and Results Section).¹⁸

The isotope-effect results are summarized in Table III. Confidence in the results is best gained by close examination of the complete details of the isotope-effect experiments; samples of our results are presented in Tables IV and V for the α - and β -carbon-14 labeled p -Cl quaternary ammonium bromides. Complete details for the other compounds and details of other aspects of the experimental work are available in the Ph.D. dissertation of JRIE.¹

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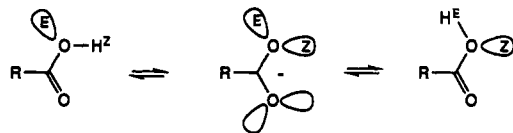
Stereoelectronic Effects at Carboxylate Oxygen: Similar Basicity of the *E* and *Z* Lone Pairs in Solution

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Abstract: Comparisons of effective molarities for intramolecular reactions and bond length– pK_a correlations show no evidence of a significant difference in basicity between the *E* and *Z* lone pairs of carboxylate in the condensed phase.

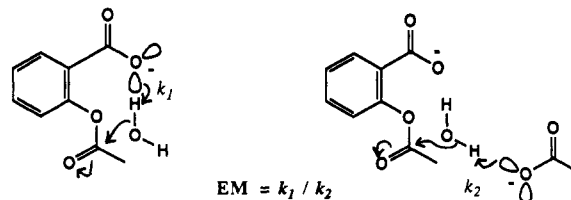
The realization¹ that the *E* and *Z* lone pairs of carboxylate may differ significantly in basicity, and thus reactivity, has inspired recent calculations²—generally supportive—and some elegant experiments³—generally inconclusive. It is the purpose of this communication to point out that there is good evidence in the literature to show that any difference cannot be large.⁴ This, together with new evidence presented below, suggests that it is not significant in solution.



1. Effective Molarities. It is suggested^{1,3} that effective molarities (EM)⁵ observed for carboxylate acting as a general base are low because the intramolecular reaction must use the (less

basic) *E* lone pair, whereas reference intermolecular processes are free to use the (more basic) *Z* lone pair of electrons. This is not supported by the evidence.

(a) Intramolecular (cyclization) reactions involving carboxylate as a nucleophile must also use the *E* lone pair, yet they show EM's that include the highest measured: typically 10⁸–10⁹ M, rising to 10¹³ M for systems in which strain in the ground state is relieved on cyclization.⁵ EM's for intramolecular general-base catalysis are typically 1–10 M. This difference is far greater than could possibly be accounted for by a stereoelectronic effect on lone pair basicity and reflects primarily the favorable free energy of formation of the ring formed in the nucleophilic reaction.



(b) Of course this argument does not rule out a contribution from such a stereoelectronic effect, which might be detected by comparing EM's for cyclizations involving carboxylate with similar reactions of other oxy anions that have only one sort of lone pair. In fact there is no discernible difference: neighboring carboxylate is certainly no less effective a nucleophile than an alkoxide or aryloxide anion.⁵

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