β-Deuterium Secondary Isotope Effects in Heterolytic Decarboxylation Reactions. Manifestations of Negative Hyperconjugation

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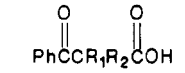
Although β-deuterium kinetic isotope effects have been recognized as useful probes of transition-state structures in carbanion-forming reactions, measurements of these effects in heterolytic decarboxylation reactions have not previously been reported. In the present study, β-deuterium secondary kinetic isotope effects and activation parameters were determined for decarboxylation of 2,2-dimethylbenzoylacetic acid. The substrates were prepared from the *tert*-butyl esters which had been prepared by a modified acetoacetic ester synthesis. The mean rate constant ratio due to substitution of deuterium in the methyl groups, k_{H_6}/k_{D_6}, is 1.052 in 0.1 M hydrochloric acid at 48.5 °C. The ratio is 1.111 for the reaction of the conjugate base at pH 10, 56.8 °C. For the substrate with only one methyl group deuterated the ratios are 1.027 and 1.07, in 1 M HCl and at pH 10, respectively. The linearity of the effect with respect to the number of deuterium substitutions indicates that the isotope effects are manifested simultaneously from the two methyl groups. Activation parameters are consistent with both reactions proceeding by the well-documented unimolecular mechanism with the higher isotope effect associated with the slower reaction. These results can be interpreted in terms of a hyperconjugative origin of the kinetic isotope effect.

β-Deuterium secondary isotope effects have been extensively utilized in analysis of reactions proceeding via electron-deficient transition states such as those that produce carbonium ions.[1-8] In these cases, hyperconjugative stabilization by adjacent protons provides a consistent basis for analysis of the isotope effect.[1] Many fewer applications have been made to electrophilic substitution reactions which involve electron-rich (carbanionic) transition states.[3] These cases require that any hyperconjugation involving hydrogens result from resonance contributions from hydride ions. Those carbanion-forming reactions for which isotope effects have been measured proceed by proton transfer from a carbon acid to a base.[3,9]

Our interest in the mechanisms of catalysis of decarboxylation led us to consider the utilization of β-deuterium secondary isotope effects to analyze transition states in these systems. Secondary kinetic isotope effects can provide valuable information about hybridization changes at reacting centers, timing of arrival at transition states, and the involvement of hyperconjugation.[10] In order to utilize such information, well-understood reactions that can be used for comparison must be available. Thus, as a basis for such analysis we have undertaken a study of β-deuterium secondary isotope effects in the decarboxylation of β-keto acids. We chose 2,2-dimethyl 3-keto acids **4–6** as substrates since their reactions are not complicated by any enol content in the reactants.[11-13] The deuterated compounds were readily prepared in an isotopically pure state by alkylation of the parent compound with trideuterioiodomethane.



1: $R_1 = R_2 = H$
2: $R_1 = CH_3; R_2 = H$
3: $R_1 = CD_3; R_2 = H$
4: $R_1 = CH_3; R_2 = CH_3$
5: $R_1 = CH_3; R_2 = CD_3$
6: $R_1 = CD_3; R_2 = CD_3$

The magnitudes of the kinetic isotope effects as a function of structure and reactivity in the reactions of **4–6** and the related activation parameters provide a basis for the evaluation of the role of negative hyperconjugation in the stabilization of unimolecular electron-rich transition states.

Experimental Section

Instruments. Proton NMR spectra were recorded on a Varian T-60 spectrometer. Chemical shifts are reported relative to an external Me_4Si reference. UV spectra were obtained with a Varian Cary 210 spectrometer. Kinetic data were collected from the spectrometer through a microprocessor-controlled interface to a Commodore 2001 (PET) computer. All reactions were conducted with samples contained in 1-cm cuvettes in the jacketed five-cell holder of the spectrometer. The temperature of the cells was maintained by circulation through the jacket of water kept within 0.1 °C of a set point by a Neslab Exacal EX-100 apparatus. The temperature of reaction solutions was determined by measuring the temperature in a blank (water) sample with a Fisher 119 meter equipped with a Yellow Springs thermistor. For isotope effect studies, samples were run simultaneously in batches by using the automatic sample changing feature of the spectrometer. Solutions were transferred with calibrated mechanical pipets.

Materials. *tert*-Butyl acetoacetate and trifluoroacetic acid were purchased from the Aldrich Chemical Co. Iodomethane was obtained from BDH Chemicals Ltd. Iodomethane-d_3 (99.5%) was from MSD Isotopes Ltd. Hydrochloric acid (1 M) was prepared by dilution of the concentrated reagent. Sodium tetraborate buffer was prepared from sodium borate monohydrate (Fisher Scientific).

Synthesis. *tert*-Butyl Benzoylacetate (Ester of 1). The procedure of Straley and Adams for the preparation of ethyl benzoylacetate was modified.[14] A mixture of 100 mL of water

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and 50 mL of hexane was placed in a 500-mL three-neck flask equipped with a mechanical stirrer and two pressure-equalizing dropping funnels. The flask was placed in an ice bath. To the cooled mixture was added 40 mL of *tert*-butyl acetoacetate and 13 mL of a solution of 66 g of NaOH in 200 mL of water. Through the two dropping funnels were added 40 mL of freshly distilled benzoyl chloride and 54 mL of the sodium hydroxide solution over 2 h with stirring. The solution was then warmed to 35 °C for 30 min. The layers were separated in a separatory funnel, and the aqueous layer was collected and treated with 16 g of ammonium chloride (stirred for 15 h). Solids were removed by filtration. Sodium chloride (18 g) was added to the solution to induce separation of phases. The organic layer was collected, and the aqueous layer was extracted with ether. The extracts combined with the organic layer were dried by addition of benzene and removal of the azeotrope by rotary evaporation. The product was distilled at 0.5 torr (115–116 °C). The proton NMR is expectedly complex due to the presence of ca. 40% of the material in the enol form. Proton NMR (neat liquid, ppm downfield from external (Me_4Si) peaks due to keto form: δ 1.07 (9 H, s, CH_3), 3.43 (2 H, s, CH_2), 6.93 (5 H, m, C_6H_5). Peaks due to enol form (relative normalized intensities are listed, the actual peaks are ca. 40% of these values based on the signals from the keto form): δ 1.17 (9 H, s, CH_3), 5.17 (1 H, s, OH), 7.33 (6 H, m, =CH, C_6H_5).

***tert*-Butyl 2,2-Dimethylbenzoylacetate (Ester of 4).** Sodium ethoxide solution (1.1 g sodium in 15 mL of absolute ethanol) was cooled to 5 °C, and 4.5 g of *tert*-butyl benzoylacetate was added. Iodomethane (10 g) which had been cooled to −17 °C was added. The reaction flask was stoppered, and after 16 h the solution was refluxed gently to assure completion of the reaction. Sodium iodide precipitated during the course of the reaction. The solution was filtered and ethanol removed by rotary evaporation. The flask was cooled to 5 °C, and the solution was neutralized with 2.7 g of ammonium chloride in 20 mL of water. The solution was extracted with two 100-mL portions of ether, and the ether extracts were combined. The aqueous layer then was acidified with 10 mL of 1 M HCl and then extracted again with ether. The combined ether extracts were dried over anhydrous sodium thiosulfate, a procedure which also removes iodine. The solution was filtered and evaporated. The resulting solid was distilled at 85–90 °C (0.2 torr), giving the product in 85% yield. The material was identical with that reported by Logue, which was prepared by reaction of 2-lithioisobutyrate with benzoyl chloride.[15] The product was recrystallized from methanol (mp 63–65 °C). Proton NMR: δ 1.40 (9 H, s), 1.60, (6 H, s), 7.50 (3 H, m), 7.86 (2 H, m).

***tert*-Butyl 2,2-Bis(perdeuteriomethyl)benzoylacetate (Ester of 6).** The synthesis was the same as at that for 4 except that iodomethane-d_3 was substituted for iodomethane. The proton NMR spectrum was the same as that of 4 with the peak at δ 1.60 absent.

***tert*-Butyl 2-Methylbenzoylacetate (Ester of 2).** The preparation was identical with that for the dimethyl derivative except that 1 equiv of sodium and 1 equiv of iodomethane were used. Ammonium chloride (1 equiv) was used in the workup. The product was distilled at 108–115 °C (0.2 torr). Yield: 85%. NMR (neat): δ 0.9 (9 H, s), 1.03 (3 H, d), 4.0 (1 H, q), 7.04 (3 H, m), 7.5 (2 H, m).

***tert*-Butyl 2-Methyl-2-(perdeuteriomethyl)benzoylacetate (Ester of 5).** The preparation was the same as that for *tert*-butyl 2-methylbenzoylacetate (2), substituting *tert*-butyl 2-methylbenzoylacetate for *tert*-butyl benzoylacetate and iodomethane-D_3 in place of the nondeuterated material.

Preparation of Samples for Kinetic Studies. The free acids 4–6 were generated from the *tert*-butyl esters in trifluoroacetic acid by using the procedure described by Logue.[15] The ester (5 mg) was added to 0.2 mL of trifluoroacetic acid and kept at room temp for 5 min. The trifluoroacetic acid was removed under high vacuum. The sample was dissolved in 1 mL of 95% ethanol and stored at −17 °C.

Kinetic Methods. Decarboxylation in Acid. The decarboxylation reactions were conducted in stoppered UV cells containing 2.8 mL of 0.1 M HCl maintained at 48.5 °C in the sample holder of the UV spectrometer. To this was added 15 μL of the substrate solution described above which had been preincubated at the reaction temperature for 30 min. The progress of the reaction was monitored through the increase in absorbance at 229 nm due to the production of phenyl isopropyl ketone.[11,12]

Initially, 39 sets of kinetic runs were conducted to determine the relative rates of decarboxylation of 2,2-dimethylbenzoylacetic acid (4) and 2,2-bis(perdeuteriomethyl)benzoylacetic acid (6). Each set consisted of simultaneous measurements on four samples (two of each substrate). Ninety-nine data points were collected for each sample with a 90-s interval. Rate constants were determined by computer-calculated fitting of the data to the integrated first-order rate equation following the method of kinetic over relaxation ("KORE") and nonlinear least-squares analysis as described by Swain et al.[16] All runs in this and other sections gave correlation coefficients greater than 0.999 999 and standard deviations of less than 2%. The ratio of the respectively averaged observed first-order rates constants (k_h/k_d) is defined as the observed kinetic isotope effect for a particular set of runs. The runs were grouped into series which were conducted on the same day, and the mean value of these was used to calculate an overall mean for the total set of 39 runs.

The procedure was repeated using sets of runs consisting of five simultaneously measured samples: one of 2,2-dimethylbenzoylacetic acid, two of 2-methyl-2-(perdeuteriomethyl)benzoylacetic acid, and two of 2,2-bis(perdeuteriomethyl)benzoylacetic acid. A series consisted of three sets of five runs and the kinetic isotope effects for the two types of deuterated samples was determined from the observed first-order rate constants and averaged for each series. Seven series were then conducted, and the mean value for the kinetic isotope effects was determined.

Decarboxylation in Basic Solution. Sodium tetraborate buffer (pH 10, 0.1 M) was prepared from 38.1 g of sodium tetraborate reagent in water and sodium hydroxide. The buffer solutions (2.8 mL) were incubated for 35 min at 56.8 °C in stoppered UV cells in the spectrometer, and then 10 μL of substrate in ethanol (2,2-dimethylbenzoylacetic acid, 2-methyl-2-(perdeuteriomethyl)benzoylacetic acid, or 2,2-bis(perdeuteriomethyl)benzoylacetic acid) was added. The solutions were incubated further for a 10 min, and then absorbance at 240 nm was recorded simultaneously every 3 min with 99 points for each sample. Ten sets of runs were conducted, and the kinetic isotope effects for each of the deuterated species vs. the nondeuterated compound were determined and the mean values for the sets were determined.

Product Analysis. The decarboxylation reactions have previously been studied and shown to produce the corresponding ketones.[11,15] The final UV spectra of the product solutions were identical with those of the expected ketones.

Results

β-Deuterium Secondary Isotope Effects on Decarboxylation of 2,2-Dimethylbenzoylacetic Acid. The rate constant for decarboxylation of 2,2-dimethylbenzoylacetic acid at 48.5 °C is 6.9×10^{-4} s^{-1}. This is consistent with the value of 5.09×10^{-4} s^{-1} obtained for the same reaction at 47.7 °C.[13] The rate constants are presented in Table I, and the isotope effects are in Table II. The isotope effect on the rate constant for decarboxylation of the compound in which one of the methyl groups is deuterated and the other is not was also measured. The mean isotope effects (Table II) are $k_{H_6}/k_{D_6} = 1.052$ (SD 0.023) and $k_{H_3D_3}/k_{D_6} = 1.024$ (SD 0.008). These results correspond to an isotope effect per deuterium substitution of 1.0089 (SD 0.0023) using the results from the hexadeuterio compound compared to the undeuterated material and 1.0090 (SD 0.0017) per deuterium using the results from the trideuterio compound compared to the undeuterated compound. The difference is less than the derived

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Table I. First-Order Rate Constants (s^{-1}) for the Decarboxylation of 2,2-Dimethylbenzoylacetic Acid (H6) and Its Trideuteriomethyl (H_3D_3) and Bis(trideuteriomethyl) (D6) Analogues at 48.5 °C

sets[a]	$10^4k_{H_6}$	$10^4k_{H_3D_3}$	$10^4k_{D_6}$
5	6.729		6.365
4	6.961		6.429
4	6.974		6.670
6	6.993		6.615
4	6.930		6.587
3	6.700		6.427
6	6.834		6.534
4	6.909		6.735
3	6.932		6.584
3	6.953	6.730	6.566
3	6.935	6.685	6.548
4	6.960	6.787	6.671
4	6.965	6.775	6.630
5	7.000	6.855	6.667
4	6.872	6.703	6.584
2	6.975	6.805	6.540
	6.911[b]	6.763[c]	6.572[d]

[a] "Sets" refers to simultaneously collected data for samples with differing isotopic compositions. [b] Mean value. Standard deviation 0.089 [c] Mean value. Standard deviation 0.060. [d] Mean value. Standard deviation 0.099.

Table II. Kinetic Isotope Effects from Data in Table I

k_{H_6}/k_{D_6}	$k_{H_6}/k_{H_3D_3}$	$k_{H_3D_3}/k_{D_6}$
1.057		
1.083		
1.046		
1.057		
1.052		
1.042		
1.046		
1.027		
1.052		
1.059	1.037	1.021
1.043	1.025	1.018
1.051	1.028	1.022
1.051	1.021	1.028
1.044	1.025	1.018
1.066	1.025	1.040
1.052[a]	1.027[b]	1.024[c]

[a] Mean value. Standard deviation 0.025. [b] Mean value. Standard deviation 0.005. [c] Mean value. Standard deviation 0.008.

standard error of the set of data.

β-Deuterium Secondary Isotope Effects on Decarboxylation of Sodium 2,2-Dimethylbenzoylacetate. The reaction in tetraborate buffer at pH 10 was monitored at 240 nm. The change in absorbance on production of the ketone is approximately 0.1 OD unit when the initial absorbance is 1.0, which is about one-quarter the change observed in the reaction of the conjugate acid. Individual first-order rate data gave correlation coefficients of not less that 0.999 999 95 and standard deviations of less than 1%. The first-order rate constant for decarboxylation in 0.1 M tetraborate buffer is 2.33×10^{-4} s^{-1} at 56.8 °C.

The isotope effects on this rate constant were determined and averaged as described in the Experimental Section, and the rate constants are summarized in Table III. The mean isotope effects (Table IV) are k_{H_6}/k_{D_6} = 1.11 (SD 0.009) and $k_{H_6}/k_{H_3D_3}$ = 1.07 (SD 0.011). These results correspond to an isotope effect on a par deuterium basis of 1.019 (SD 0.002) using the results from the hexadeuterio compound and 1.021 (SD 0.004) per deuterium using the results from the trideuterio compound. The differences in the values are smaller than the uncertainty in the measurements.

Activation Enthalpy and Entropy for Decarboxylation. The rate constants for decarboxylation of 2,2-dimethylbenzoylacetic acid in 0.1 M HCl and in pH 10 buffer at four temperatures are summarized in Table V. Plots of ln k/T vs. $1/T$ were used to determine activation parameters. For the acid solution, the slope of the linear plot (least-squares fit) is 11 140 K (SD 120) with a correlation coefficient of 0.9997. The slope is $\Delta H^{\ddagger}/R$, giving an enthalpy of activation of 22.2 kcal/mol.[17] For the pH 10 reaction, the enthalpy of activation is 23.2 kcal/mol (SD 1.4). Entropies of activation were determined from the intercept of the plot according to eq 1, where k is Boltzmann's constant, h is Planck's constant, and R is the gas constant.[17] The entropy of activation of the decarboxylation reaction in 0.1 M HCl is −4.41 cal/mol/deg (SD 0.72). The decarboxylation reaction at pH 10 has an entropy of

$$\Delta S^{\ddagger} = (\text{intercept} - \ln k/h)(R) = (\text{intercept} - 23.76)(1.987) \quad (1)$$

Table III. First-Order Rate Constants (s^{-1}) for the Decarboxylation of Sodium 2,2-Dimethylbenzoylacetate (H_6) and Its Trideuteriomethyl (H_3D_3) and Bis(trideuteriomethyl) (D_6) Analogues at 56.8 °C, pH 10, 0.1 M Borate Buffer

run[a]	$10^4k_{H_6}$	$10^4k_{H_3D_3}$	$10^4k_{D_6}$
1	2.35		2.10
2	2.34		2.08
3	2.34		2.08
4	2.30		2.09
5		2.18	2.07
6		2.18	2.07
7		2.19	2.07
8	2.36	2.23	2.13
9	2.32	2.15	2.10
10	2.30	2.17	2.07
	2.33[b]	2.18[c]	2.09[d]

[a] Each run consists of a total of five samples with average values reported for identical samples. For runs 1–7 there were three members of the sample from the species in the left column and two form that in the right column. For runs 8–10 the distribution is 2, 2, 1. [b] Mean value. Standard deviation 0.024. [c] Mean value. Standard deviation 0.026. [d] Mean value. Standard deviation 0.019.

Table IV. Kinetic Isotope Effects from Data in Table III

k_{H_6}/k_{D_6}	$k_{H_6}/k_{H_3D_3}$	$k_{H_3D_3}/k_{D_6}$
1.12		
1.12		
1.12		
1.10		
		1.05
		1.05
		1.06
1.11	1.06	1.05
1.10	1.08	1.02
1.11	1.06	1.05
1.11[a]	1.07[b]	1.05[c]

[a] Mean value. Standard deviation 0.009. [b] Mean value. Standard deviation 0.011. [c] Mean value. Standard deviation 0.014.

Table V. Effect of Temperature on Observed First-Order Rate Constant for Decarboxylation of 2,2-Dimethylbenzoylacetic Acid

acidity	T, °C	10^5k, s^{-1}
0.1 M HCl	25.0	3.7
	48.5	69.0
	63.0	300
	79.0	1400
pH 10	56.8	23.0
	67.5	79.9
	75.4	159.9

(17) Hirsch, J. A. *Concepts in Theoretical Organic Chemistry*; Allyn and Bacon: Boston, 1974; p 124.

activation of −4.9 cal/mol/deg (SD 2.4).

The decarboxylation reaction of the acid has a small entropy of activation which is consistent with expectations for transition states in which a single molecule is converted to two molecules.[18] The conversion of the conjugate base has a larger entropy of activation consistent with the involvement of hydrogen bonding by the solvent in stabilizing the incipient enolate which is generated in the transition state.

For comparison, Hay and Tate studied the temperature dependence of the decarboxylation of benzoylacetic acid in acidic and basic dioxane.[19] The entropy of activation for decarboxylation of the conjugate base (5 cal/mol/deg) is 11 units more negative than that of the conjugate acid, consistent with the poor solvation of ionized material in the less polar solvent.

Discussion

Mechanisms and Isotope Effects. The decarboxylation of the acid and of the conjugate base show different β-deuterium isotope effects. In both cases the α-carbon atom is converted from sp^3 hybridization to sp^2 hybridization during the course of the reaction with the transition state partially rehybridized. Changes in the vibrational force constants arising from delocalization of electron density into the methyl groups result in an isotope effect on the rate constant for decarboxylation due to the smaller energy level differences in the transition state between the deuterated and undeuterated species.[4] Since the hydrogens are more weakly held in the transition state, the lighter isotope is preferentially distributed in the transition state, yielding a positive effect.[1] The larger isotope effect in the case of the conjugate base is consistent with greater stabilization of the less stable transition state.[20]

The magnitude of the isotope effect depends on the amount of π or carbanion character at the transition state and the extent to which the methyl groups interact with the developing π system. The methyl groups stabilize the transition state by accepting electron density into the C–H antibonding orbitals ("negative" hyperconjugation[4,21,22]). In the case of carbonium ion formation, the methyl group can donate electron density ("positive" hyperconjugation; Buddenbaum and Shiner have presented an analysis of the origin of these and related effects[23]). Examination of possible resonance structures for the reactants, products, and transition states does not indicate any function for electron donation since structures involving positive hyperconjugation have destabilizing effects, generating additional negative charge at the reaction center. Since decarboxylation is an electrophilic substitution process, electron withdrawal is necessary to promote the reaction. Therefore, any stabilization through hyperconjugation must be of the negative variety.

The only other study of β-deuterium isotope effects on decarboxylation reactions of which we are aware is that of the thermal reaction of β-peroxy lactones.[24] For these reactions, which proceed via the formation of radicals, there was no isotope effect observed. A more suitable reaction to compare to ionic decarboxylation is proton transfer from carbon acids. Matsson studied the β-deuterium isotope effect on the amine-catalyzed prototopic rearrangement of 1-methylindene in toluene and in dimethyl sulfoxide.[25] He found an isotope effect of 1.033 (per deuterium in the methyl group) for the reaction in toluene and an isotope effect per deuterium of 1.028 in dimethyl sulfoxide. This is consistent with either an earlier transition state in dimethyl sulfoxide or stabilization of the incipient carbanion by the more polar solvent leading to a smaller isotope effect due to less internal demand for stabilization. The primary isotope effect on this proton-transfer reaction is larger in dimethyl sulfoxide which is consistent with an earlier transition state. (The proton transfer to the amine is endothermic and so an unsymmetrical transition state resembling the product is expected. An earlier transition state will decrease the asymmetry and is likely to increase the isotope effect.[8,22]) Therefore, an earlier transition state is a consistent explanation for the differences in magnitude.

Reactivity and the Magnitude of the Isotope Effect. The gas-phase acidities of acids that are subject to β-deuterium isotope effects have been measured.[3] The isotope effects show little variation, and they do not follow the acidities. Shiner et al. measured the β-deuterium isotope effect on the solvolysis rates of phenyl-substituted 1-phenylethyl halides.[26] The isotope effect increases from 1.11 for the compound with the most electron-donating substituent to 1.22 for the unsubstituted compound. This is consistent with an interpretation that the isotope effect measures the degree of stabilization by hyperconjugation. The highest energy transition state is subject to the greatest extent of hyperconjugative stabilization.[20]

In the two systems that were evaluated in the present study, the larger isotope effect is observed for the decarboxylation of the conjugate base which is also slower to react. This is consistent with a hyperconjugative origin of the isotope effect but is not a unique interpretation since interactions in transition states are certain to be complex.[23]

The isotope effect per deuterium for rearrangement of 1-methylindene[25] is about 50% larger than for the decarboxylation of the conjugate base of 2,2-dimethylbenzoylacetic acid. Since the reactions are very different, one cannot pinpoint the source of the factor. For example, the carbanion generated in the decarboxylation is stabilized as an enolate, causing a lowered demand for stabilization by other substituents. Decreased charge development lessens the amount of sp^2 relative to sp^3 character of the transition state. Decreased change in hybridization is consistent with smaller secondary isotope effects. The decarboxylation in water involves a solvent that is particularly good for anions and may produce a smaller demand for stabilization by internal groups than the cases involving poorer solvents. Yet another explanation could be that the 1-methylindene has only a single α-methyl substituent while the β-keto acid has two methyl substituents. The single substituent may interact more strongly than two substituents whose influence is shared, analogous to the outcome of cross-conjugation.

Cumulative Isotope Effects on Decarboxylation. The total isotope effect we measure for the bis(trideuteriomethyl) derivative is about twice as large as that for the (trideuteriomethyl)methyl derivative. This cu-

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mulative behavior is consistent with the isotopes acting independently. In terms of hyperconjugation, two interactions should occur simultaneously. If the more stabilizing (H rather than D) interaction were to dominate, then in the case of the trideuterio substrate we would have expected to see an isotope effect much less than half that for the hexadeuterio species. Thus, for this system the "rule of the geometric mean"[1,27] is applicable and the isotope effect can be interpreted on a "per deuterium" basis.

Conclusion

We can expect that other heterolytic decarboxylation reactions will show positive β secondary kinetic isotope effects and that reactivity will be a major determinant of the magnitude of the effect. The effect should also be additive for multiply deuterated species. Thus, for complex mechanisms in which decarboxylation is rate-determining, the isotope effect can be used to elucidate the relative magnitudes of this step and those preceding it.[26] However, knowledge of details and empirical correlations of the isotope effect as a function of structure and reactivity will require that results be obtained for many more compounds.

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Registry No. 1 *t*-Bu ester, 54441-66-6; 2 *t*-Bu ester, 104015-38-5; 4, 38744-73-9; 4 *t*-Bu ester, 53935-56-1; 5 *t*-Bu ester, 104034-35-7; 6 *t*-Bu ester, 104015-37-4.

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Synthesis of a C-15-Substituted Porphyrin from a b-Bilene Precursor

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The synthesis of a porphyrin substituted at C-13 with an ethoxycarbonyl residue and at C-15 with a β-(methoxycarbonyl)methyl side chain was attempted using a b-meso-substituted b-bilene-1′,8′-di-*tert*-butyl ester precursor. The latter was obtained by condensation of *tert*-butyl 3,3′-dimethyl-4-(β-acetoxyethyl)-4′-[β-(ethoxycarbonyl)ethyl]dipyrrylmethane-5-carboxylate with *tert*-butyl 3′,4-dimethyl-3-ethyl-4′-(ethoxycarbonyl)-5′-[α-oxo-β-(ethoxycarbonyl)ethyl]dipyrrylmethane-5-carboxylate. Although the b-bilene was obtained in 60% yield, its cyclization to the porphyrin using ethyl orthoformate in acid medium gave poor yields (4%), very likely due to steric interactions between the meso substituent and the ethoxycarbonyl residue.

Of the many porphyrin total syntheses which have been proposed in the recent literature only a few are useful and versatile enough to be considered as general procedures for porphyrin synthesis.[1] The use of b-bilene-1′,8′-dicarboxylates appeared to be one of them since b-bilenes could be obtained in good yields by the condensation of two pyrrylmethane halves,[2] and b-bilene-1′,8′-di-*tert*-butyl esters (see Scheme I) could be cyclized to porphyrins by treatment with trifluoroacetic acid (cleavage of the *tert*-butyl esters) followed by cyclization using trichloroacetic acid and trimethyl orthoformate as the one-carbon linking unit.[3] A b-bilene was a short-lived intermediate in the total synthesis of chlorin-e_6,[4] and a b-bilene which carried a fused cyclopenteno ring from C-13 to C-15 was also the synthetic precursor of deoxophylloerythroetioporphyrin.[5] In the latter case, however, although the synthesis of the meso-substituted b-bilene was achieved in good yields, its cyclization to the porphyrin took place in only 6% yield. This low yield was attributed to the steric factors introduced by the isocyclic ring. We therefore decided to explore the synthesis of the C-15-substituted porphyrin **4** from the b-meso-substituted b-bilene **3** (Scheme I). Porphyrin **4** (2-β-hydroxyethyl)chloroporphyrin-e_6 triester) could be regarded as a useful precursor of 2-vinylpheoporphyrin-a_5 dimethyyl ester[1a] since the cyclopentanone ring could be easily formed by a Dieckmann-type condensation, while the vinylization of the β-hydroxyethyl residue is a well-known procedure.[1g] There should be no strain in the cyclization of **3** to **4** which could be attributed to the isocyclic ring, thus eliminating what appeared to be the main hindrance in the synthesis of porphyrins which carry a cyclopentanone ring bridging the C-13 and C-15 positions.

The synthesis of the b-meso-substituted b-bilene **3** was approached by attempting the condensation of two dipyrrylmethane halves, one of which carried a β-oxopropionate residue at the C-5′ position (Scheme I). The synthesis of each dipyrrylmethane moiety required the use of extensive pyrrole chemistry which will be discussed below. The prior synthesis of dipyrrylmethane **9** was planned to obtain the dipyrrylmethane **1**, since the latter

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