suggest that such a variation may not necessarily produce an abnormal coefficient. Further calculations for other families of carbon acids are needed.

Acknowledgment. A generous grant of computing time from the Memphis State University Computing Center is gratefully acknowledged.

Registry No. CH$_3$NO$_2$, 75-52-5; CH$_3$CH$_2$NO$_2$, 79-24-3; CH$_3$(CH$_2$)$_2$NO$_2$, 108-03-2; CH$_3$CH(CH$_3$)NO$_2$, 79-46-9; C$_2$H$_5$CH(CH$_3$)NO$_2$, 600-24-8; CF$_3$H, 75-46-7; (CF$_3$)$_2$CFH, 431-89-0; (CF$_3$)$_3$CH, 382-24-1; hydroxide, 14280-30-9; methoxide, 2143-68-2.

Heavy-Atom Isotope Effects on the Acid-Catalyzed Hydrolysis of Methyl Benzoate[1]

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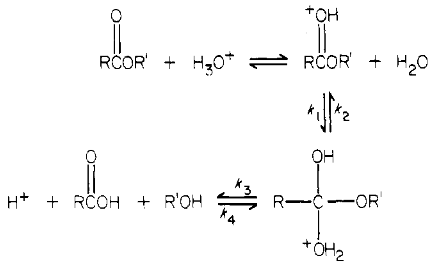
The acid-catalyzed hydrolysis of most esters occurs by way of a tetrahedral intermediate[2] (eq 1). Carbonyl oxygen exchange between ester and solvent accompanies the hydrolysis of many esters.[3] Exchange is invariably slower than hydrolysis, indicating that the formation of the tetrahedral intermediate is probably rate determining ($k_3 > k_2$).



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Heavy-atom isotope effects are useful probes of transition-state structure in organic reactions.[4] Oxygen isotope effects on the alkaline hydrolysis of methyl benzoate,[5,6] methyl formate,[7] and acetyl tryptophan methyl ester[5] are indicative of an early transition state in which extensive changes in bonding have not occurred. Carbonyl carbon isotope effects on the hydrolysis of benzoate esters[6,8] are consistent with this conclusion. The only previous study of a heavy-atom isotope effect on the acid-catalyzed hydrolysis of an ester is that of Sawyer and Kirsch,[7] who reported an ether oxygen isotope effect k^{16}/k^{18} = 1.0009 for the acid-catalyzed hydrolysis of methyl formate at 25 °C.

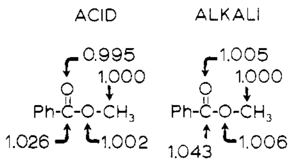

Figure 1. Summary of isotope effects on the acid-catalyzed hydrolysis of methyl benzoate in aqueous solution at 91 °C (this work) and the alkaline hydrolysis of methyl benzoate in aqueous solution at 25 °C (ref 5).

We have recently described a double-label method for measuring heavy-atom isotope effects which permits measurement of isotope effects at sites which are not amenable to study by the direct isotope-ratio technique.[5,6] In this paper we report studies by this technique of four heavy-atom isotope effects on the acid-catalyzed hydrolysis of methyl benzoate.

Results

Ether oxygen and methyl carbon isotope effects on the acid-catalyzed hydrolysis of methyl benzoate at 91 °C in aqueous 0.2 M H$_2$SO$_4$ were measured by the usual natural-abundance isotope-ratio technique. The results are summarized in Table I.

The carbonyl oxygen isotope effect on the acid-catalyzed hydrolysis of methyl benzoate was measured by the pseudo-natural-abundance double-label method.[5] [*methyl*-^{13}C]Methyl [*carbonyl*-^{18}O]benzoate was mixed with isotopically depleted [*methyl*-^{12}C]methyl benzoate in the proportion 1:90 to produce ester having the usual abundance of ^{13}C in the methyl group, but have ^{18}O in the carbonyl oxygen of those molecules containing ^{13}C in the methyl group. Measurement of the "methyl-^{13}C" isotope effect on this material gives, after small corrections, the product of the methyl-^{13}C and carbonyl-^{18}O isotope effects.[5] Results are summarized in Table I. Because the methyl-^{13}C and ether-^{18}O isotope effects are so small, no corrections were necessary for the small amount of ^{18}O present in the ether oxygen position of the doubly labeled compound or for the methyl carbon isotope effect. Based on results obtained with ethyl benzoate,[3b] the amount of carbonyl-^{18}O exchange during the hydrolysis should be so small as to render correction for depletion of this label unnecessary.

The carbonyl carbon isotope effect on the acid-catalyzed hydrolysis of methyl benzoate was also measured by the pseudo-natural-abundance double-label method, using a mixture of [*methyl*-^{13}C]methyl[carbonyl-^{13}C]benzoate and isotopically depleted [*methyl*-^{12}C]methyl benzoate. The results are summarized in Table I.

Discussion

Heavy-atom isotope effects on the acid-catalyzed hydrolysis of methyl benzoate which have been measured in this study are summarized in Figure 1, along with the corresponding isotope effects for the alkaline hydrolysis.[5] The ether oxygen isotope effect on the acid-catalyzed hydrolysis of methyl benzoate (k^{16}/k^{18} = 1.002) is similar in magnitude to the ether oxygen isotope effect on the acid-catalyzed hydrolysis of methyl formate[7] (1.0009 at 25 °C).

We assume that the hydrolysis of methyl benzoate proceeds by way of a tetrahedral intermediate (cf. eq 1). A small amount of oxygen exchange with the solvent accompanies the hydrolysis.[3b] The small amount of exchange observed indicates that formation of the tetrahedral in-

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(1) This research was supported by Grants PCM75-15315 and PCM77-00812 from the National Science Foundation. Professor Paul Bender provided useful advice concerning isotope-ratio measurements.

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Table I. Isotope Effects on the Acid-Catalyzed Hydrolysis of Methyl Benzoate at 91 °C in Aqueous 0.2 M H_2SO_4

		isotope ratios[a] × 10^6		
isotope studied	% reacn	low conversion	high conversion	isotope effect[b]
		m/e 30/28		
ether-O	32	2842	2850	1.0034
	30	2843	2849	1.0025
	30	2848	2851	1.0013
				mean 1.0024 ± 0.0011
		m/e 29/28		
methyl-C	32	13 817	13 819	1.0002
	30	13 810	13 815	1.0004
	30	13 814	13 818	1.0003
				mean 1.0003 ± 0.0001
		m/e 45/44		
carbonyl-O	31	12 525	12 473	0.9945
	28	12 495	12 457	0.9961
	32	12 509	12 465	0.9953
	35	12 524	12 464	0.9933
				mean 0.9948 ± 0.0012
		m/e 45/44		
carbonyl-C	26	11 563	11 749	1.0234
	31	11 546	11 753	1.0271
	31	11 532	11 747	1.0227
				mean 1.0262 ± 0.0025

[a] Decade settings from the isotope ratio mass spectrometer for the ratio m/e 30/28, 29/28, or 45/44, corrected to a constant value of the reference standard but not otherwise corrected. [b] Calculated isotope effect $k^{\text{light}}/k^{\text{heavy}}$ corrected for other isotopic species and for percent reaction. See ref 5 for details.

termediate, rather than its decomposition, is rate-determining.[9] The small magnitude of the ether oxygen isotope effect on the hydrolysis is consistent with this conclusion. Large isotope effects (1.04–1.06) are observed in cases where decomposition of the tetrahedral intermediate is rate determining.[5,7]

The relationship between the observed isotope effects and the isotope effects on the individual steps of the mechanism of eq 1 is complex,[5] but provided that formation of the tetrahedral intermediate is nearly wholly rate determining ($k_3 \gg k_2$) the observed isotope effects will be nearly equal to the isotope effects on k_1. Qualitatively, isotope effects in this system reflect changes in bonding to the isotopic atom between ground state and transition state. Increased bonding at the transition state will tend to make isotope effects inverse ($k/k^* > 1$), whereas decreased bonding will tend to make isotope effects normal ($k/k^* > 1$). A more quantitative description of isotope effects requires inclusion of the "imaginary frequency factor",[12] which is always ≥1.

The smaller magnitudes of the isotope effects in the acid-catalyzed hydrolysis of methyl benzoate compared to those in the alkaline hydrolysis (cf, Figure 1) can qualitatively be interpreted as being due to a greater degree of bonding in the transition state for the acid-catalyzed reaction. This is most clearly seen in the case of the carbonyl oxygen, which shows a normal isotope effect in alkali but an inverse isotope effect in acid. The transition state for the acid-catalyzed hydrolysis probably looks very much like the protonated ester, with little reduction in carbon–oxygen bond order.

The small magnitude of the ether oxygen effect is also consistent with the idea that the transition state for formation of the tetrahedral intermediate is early. We have previously argued that a significant equilibrium isotope effect on tetrahedral-intermediate formation is to be expected for the ether oxygen.[5] The lack of a significant kinetic isotope effect in the acid-catalyzed hydrolysis argues that the transition state is relatively reactant-like, with little change in bonding to the ether oxygen.

Precise interpretation of carbonyl carbon isotope effects on ester hydrolysis and related reactions is enigmatic at present, but calculations of Buddenbaum and Shiner[10] indicate that the isotope effect is near unity for a reactant-like transition state and gradually increases as the transition state becomes more like the tetrahedral intermediate. The small magnitude of the carbon isotope effect on the acid-catalyzed hydrolysis of methyl benzoate compared to isotope effects on other reactions of methyl benzoate is consistent with the suggestion above that the transition state is relatively reactant-like.

In conclusion, isotope effects on the acid-catalyzed hydrolysis of methyl benzoate are consistent with the idea that the formation of the tetrahedral intermediate is rate determining and the transition state for the reaction is relatively early.

Experimental Section

Materials. The preparation and purification of the various isotopically enriched and depleted methyl benzoates was described earlier.[5] Norit was purified by heating at 1000 °C in a quartz tube under high vacuum. Water for these experiments was purified by a Millipore Q filtration system. The resistance of this water was at least 18 megohms.

Methods. Kinetic measurements were made with a Gilford Model 222 spectrophotometer. Constant reaction temperature was maintained with a Tempunit Model TU-12 constant-temperature bath filled with mineral oil. Gas chromatography was done on a Varian Model 90P-3 gas chromatograph equipped with a thermocouple detector and a 20% TCEP on Chromosorb P column (15 ft × $^3/_8$ in.). Pyrolysis of methanol to either carbon monoxide or carbon dioxide was done by using the apparatus described by Borowitz et al.[11] Isotopic analyses were done on a Nuclide Associates RMS 6-60 isotope-ratio mass spectrometer with a dual-inlet system.

Isotope Effect Procedure. For each experiment, 325 mL of a solution which was 0.2 M in sulfuric acid and 4 mM in methyl benzoate was prepared. This solution was split into a 250-mL and a 75-mL portion.

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(9) This assumes that the lifetime of the tetrahedral intermediate is sufficiently long that proton transfers among the various oxygens of the tetrahedral intermediate are at equilibrium.

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(12) Reference 4g, p 45.

The larger portion was placed in a glass ampule and sealed with a torch. The ampule was then placed in the constant-temperature bath at 91 °C for 2 h, after which it was removed from the bath and cooled by immersing in cold water. The extent of reaction was determined by withdrawing a small aliquot and measuring the optical densities at both 248 and 259 nm. These optical densities were then compared to those for complete reaction. The infinity points were measured independently for known concentrations of methyl benzoate under the experimental conditions of the isotope effect experiments. Approximately the same slit width was used for all experiments, and the extinction coefficient change resulting from hydrolysis was found to be 44.7 M^{-1} cm^{-1} at 259 nm and 221 M^{-1} cm^{-1} at 248 nm. After determination of percent reaction, the reaction solution was neutralized with KOH and extracted twice with 2-g portions of Norit. The Norit was filtered off after each extraction with Whatman No. 42 filter paper.

To the smaller 75-mL portion was added enough freshly prepared KOH to bring the pH around 13. Hydrolysis was allowed to proceed beyond 10 half-lives, after which the solution was neutralized with sulfuric acid, diluted to 250-mL total volume, and extracted with Norit as described above. At this point the large and small portions were treated in an identical manner.

The remaining procedure for concentration, purification, and chemical conversion of the methanol to either carbon monoxide or carbon dioxide is identical with that which we have previously published.[5]

Registry No. Methyl benzoate, 93-58-3.

Rearrangements and Demethylation of 2-*o*-Anisyl-2-*endo*-fenchyl Alcohol

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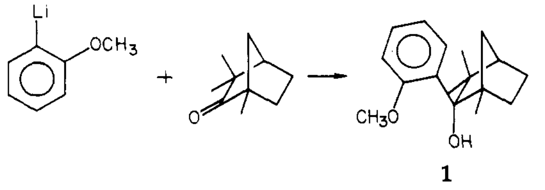
As part of a plan to prepare chiral compounds for studies in asymmetric synthesis, we have attempted the chlorination of the title compound by several methods and have observed some unusual chemical results which we now report.

Addition of (+)-fenchone to *o*-anisyllithium gave alcohol product consisting of a single isomer in 82% isolated yield. On the basis of analogy with the formation of 2-*p*-anisyl-2-*endo*-camphenilol by exo attack of *p*-anisylmagnesium bromide on the structurally similar ketone camphenilone,[1-3] the structure of this alcohol was assigned that of 2-*o*-anisyl-2-*endo*-fenchyl alcohol (1, eq 1). All spectral and analytical data were consistent with that assignment (see Figure 1).



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An attempt was made to chlorinate 1 using an adaptation of the method of Brown and Rei.[4] Passage of anhydrous hydrogen chloride gas through a chloroform solution of 1 at 25 °C resulted in the formation of two new products 2 and 3. The reaction was followed by VPC: 2 was formed first and changed into 3 with time under the reaction conditions. The conversion of 2 to 3 was slowed when the reaction was run at 0 or −60 °C, but it was not stopped.

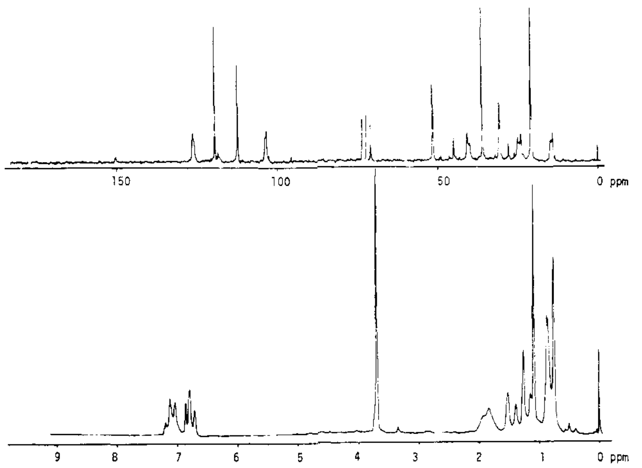
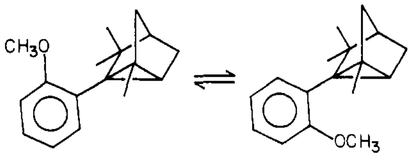


Figure 1. Upper trace: 22.5-MHz ^{13}C NMR spectrum of 2, completely decoupled, 301 K, 5000-Hz sweep width. Lower-trace: 90-MHz ^{1}H NMR spectrum of 2, 301 K, 1000-Hz sweep width.

Phosphorus pentachloride and calcium carbonate, a reagent combination which rapidly leads to chlorination with retention of configuration in many,[5] but not all,[6] tertiary alcohols, gave the same pair of products, 2 and 3, when alcohol 1 was added. The only difference between this reaction system and use of anhydrous hydrogen chloride was that the conversion of 2 to 3 was slow even at room temperature with the $PCl_5/CaCO_3$ combination.

A reaction mixture containing components 2 and 3 was separated by silica gel chromatography. Compound 2 was eluted first with pentane and was then purified into a colorless oil by preparative VPC. Compound 3 was eluted from the column with diethyl ether and, following Kugelrohr distillation, formed snow-white crystals.

Microanalyses of both 2 and 3 showed that both were devoid of chlorine and contained only carbon, hydrogen, and oxygen. Both the proton NMR and the completely decoupled carbon-13 NMR spectra of 2 showed uncharacteristically broad signals (Figure 1). The broadness of the signals suggested the existence of two rotational isomers of 2 which interconvert slowly enough at ambient probe temperature (301 K) for signals of the nuclei of both isomers to be seen. Indeed, at 273 K, every signal in the carbon-13 NMR spectrum of 2 was split into two signals. On the basis of the spectral data, the assignment of the two rotational isomer structures 2 and 2′ was made for this compound.



2 2′

The coalescence temperature of the pair of signals in the carbon-13 spectrum of 2 centered at δ 15.3 ($\Delta\nu = 19.5$ Hz) was found to be 318 K (Figure 2). From this an activation

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