

CH=CHOCH₃, OCHH), 3.58 (s, OCH₃), 3.05 (dt, *J* = 15.8, 5.4 Hz, OCH₂CHH), 2.36 (s, ArCH₃), 1.06 (dtd, *J* = 15.8, 10.1, 2.2 Hz, OCH₂CHH).

A sample of *trans*-6 for ¹³C NMR analysis was prepared by photolysis of a CD₂Cl₂ (1 mL) solution of *trans*-5 (40 mg, 0.076 mmol) in a 10-mm septum-capped NMR tube for 42 h at -78 °C under N₂ purge. Cr-(acac)₃ (32 mg, 0.07 M) was then added, and the tube was sealed under high vacuum: ¹³C{¹H} NMR (50.1 MHz, -45 °C) δ 311.2 (W=C), 210.9, 210.6, 207.9, 203.1 (CO), 148.7, 143.1 (ipso, para), 128.3 (ortho, meta, CH=CHOCH₃), 80.4 (OCH₂), 61.0 (CH=CHOCH₃), 60.2 (OCH₃), 28.6 (OCH₂CH₂), 21.2 (ArCH₃). A ¹³C{¹H} INEPT experiment (90.56 MHz, -35 °C) confirmed the assignment of resonances at δ 128.2, 128.0 (unresolved in 50.1 MHz spectrum above), and 61.0 as methine carbons. A two-dimensional ¹³C-¹H correlation spectrum (decoupled in F1 and F2)²² was obtained on a Bruker AM-360 spectrometer at -35 °C. The spectrum showed the ¹³C signal at δ 128.2 consisted of two resonances: an aromatic CH coupled to the proton at δ 7.21 and the vinyl ether carbon CH=CHOCH₃ coupled to the vinyl H at δ 6.47 in the ¹H NMR spectrum.

An IR spectrum of a 0.011 M solution of *trans*-6 in CH₂Cl₂ (generated by photolysis of *trans*-5 at -78 °C for 20 h) was obtained at -78 °C: 2015 (s), 1929 (s), 1909 (s), 1884 (s) cm⁻¹. An IR sample in hexane was prepared by evaporation of CH₂Cl₂ from a sample of *trans*-6 (prepared by photolysis of *trans*-5 at -78 °C for 31 h) at -15 °C under high

vacuum and addition of hexane at -78 °C. The sample was warmed to -15 °C and an IR spectrum was obtained at -78 °C: 2026 (m), 1945 (m), 1918 (s) cm⁻¹.

Photolysis of *cis*-5: Generation of (CO)₄W=C-(OCH₂CH₂CH=CHOCH₃)C₆H₄-*p*-CH₃ (*cis*-6). CD₂Cl₂ (0.3 mL) was distilled under high vacuum into a 5-mm NMR tube containing *cis*-5 (12 mg, 0.023 mmol). Photolysis at -78 °C for 21 h generated a (9:1) mixture of *cis*-6 and *cis*-5 as determined by ¹H NMR.

For *cis*-6: ¹H NMR (CD₂Cl₂, -35 °C) δ 7.94 (d, *J* = 8.3 Hz, 2 H, C₆H₄), 7.27 (d, *J* = 8.1 Hz, C₆H₄), 6.92 (d, *J* = 5.2 Hz, CH=CHOCH₃), 5.46 (ddd, *J* = 10.8, 4.6, 2.8 Hz, OCHH), 4.31 (td, *J* = 10.9, 2.8 Hz, OCHH), 3.83 (s, OCH₃), 2.90 (dt, *J* = 8.3, 5.2 Hz, CH=CHOCH₃), 2.66 (ddt, *J* = 13.6, 5.3, 2.9 Hz, OCH₂CHH), 2.36 (s, ArCH₃), 2.20 (tdd, *J* = 13.0, 8.6, 4.7 Hz, OCH₂CHH); ¹³C NMR (125.76 MHz, -80 °C) δ 318.2 (W=C), 214.0, 209.7, 201.0, 199.6, 197.4 (CO, *cis* CO of remaining *cis*-5), 148.3, 144.1 (ipso, para), 129.3, 128.7 (ortho, meta), 128.5 (CH=CHOCH₃), 82.6 (OCH₂), 61.0 (C-H=CHOCH₃), 56.7 (OCH₃), 23.7 (OCH₂CH₂), 21.5; IR (hexane) 2024 (m), 1931 (m), 1916 (s) cm⁻¹.

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Parallel Behavior in Kinetic and NMR Effects: Secondary Deuterium Isotope Effects on the Alkaline Hydrolysis of Esters

Michael S. Matta,* Dale E. Broadway, and Michele K. Stroot

Contribution from the Department of Chemistry, Southern Illinois University at Edwardsville, Edwardsville, Illinois 62026. Received November 14, 1986

Abstract: β-Deuterium secondary kinetic isotope effects (β-D KIEs) on the alkaline hydrolysis of the *p*-nitrophenyl esters of acetic, propanoic, butanoic, and pentanoic acids in pH 10.70, 0.20 M carbonate buffer at 25 °C tend to increase with increasing chain length of the esters up to the pentanoate. The β-D KIEs are respectively 0.975 ± 0.004, 0.960 ± 0.002, 0.940 ± 0.001, and 0.948 ± 0.004. The activation energies of the esterolyses of the isotopically light esters follow a similar pattern, as do the ¹³C NMR nuclear shieldings in CDCl₃ of the isotopically light parent carboxylic acids (20.9, 27.4, 35.9, and 33.8 (ppm)) and ¹³C NMR one-bond isotope shifts produced by disubstitution of deuterium for hydrogen at the α-carbons of the acids (0.45, 0.55, 0.60, and 0.59 (ppm)). Correlation of nuclear shieldings and isotope shifts is known from previous work. The possibility is considered that all of the kinetics-based and NMR relationships are linked through the operation of a common ground-state feature of the ester and acid alkyl chains.

The chemical literature contains a growing number of theoretical and experimental studies of NMR isotope shifts resulting from the substitution of deuterium for hydrogen on carbon.¹ These studies complement a substantial literature concerning secondary kinetic isotope effects on organic reactions.² The possibility of a correlation between kinetic and NMR isotope effects has been mentioned.^{1a} To the best of our knowledge, however, no experimental study of this kind has been done. Thus,

having determined the β-deuterium secondary kinetic isotope effects (β-D KIEs) on the alkaline hydrolysis of the *p*-nitrophenyl esters (NPEs) of the C₂-C₅ normal alkanolic acids, we were interested in comparing them with NMR isotope shifts at α-carbon of the esters. Technical difficulties prevented determination of the shifts for the esters, but we were able to measure the nuclear shieldings, isotope shifts, and C-D coupling constants at the α-carbons of the parent acids. Here we report these kinetic and NMR investigations.

Results

Second-order rate constants for the alkaline hydrolysis of NPEs of the homologous C₂-C₅ normal alkanolic acids and their α-deuterated versions are given in Table I, as are the β-D KIEs. The value *k*_{3H}/*k*_{3D} of 0.975 ± 0.004 found in this study for the acetate is identical within experimental error to the 0.970 ± 0.009 reported by Kovach and co-workers.^{3,4}

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(4) The apparent second-order rate constants of Table I were obtained by dividing the pseudo-first-order rate constants by *a*_{OH}, a procedure that ignores contributions of the rate of hydrolysis by nucleophilic buffer species. The similarity of *k*_{3H}/*k*_{3D} for *p*-nitrophenyl acetate found by us (0.20 M bicarbonate/carbonate buffer) and by Kovach and co-workers³ (unbuffered solution, ionic strength 1.0 M (KCl)) indicates that contributions to catalysis by buffer nucleophiles do not have a measureable effect on the β-D KIEs.

Table I. β -Deuterium Secondary Kinetic Isotope Effects on the Alkaline Hydrolysis of *p*-Nitrophenyl Esters^a

<i>p</i> -nitrophenyl ester	k , M ⁻¹ s ⁻¹	k_H/k_D
acetate	22.92, 22.67, 22.67 av 22.76 ± 0.08	
acetate- <i>d</i> ₃	23.41, 23.41, 23.17 av 23.22 ± 0.08	0.979, 0.968, 0.978 av 0.975 ± 0.004 ^b
propanoate	19.89, 20.07, 19.89 av 19.95 ± 0.06	
propanoate- α - <i>d</i> ₂	20.79, 20.79, 20.75 av 20.78 ± 0.01	0.957, 0.965, 0.959 av 0.960 ± 0.002
butanoate	12.52, 12.28, 12.13 av 12.31 ± 0.11	
butanoate- α - <i>d</i> ₂	13.30, 13.06, 12.92 av 13.09 ± 0.11	0.941, 0.940, 0.939 av 0.940 ± 0.001
pentanoate	12.11, 12.11, 12.11 av 12.11 ± 0.00	
pentanoate- α - <i>d</i> ₂	12.86, 12.77, 12.68 av 12.77 ± 0.05	0.942, 0.948, 0.955 av 0.948 ± 0.004

^a Ester concentration approximately 5×10^{-5} M in 0.20 M carbonate buffer of pH 10.70, 25 ± 0.1 °C; all reaction mixtures contained 3.2% CH₃CN; H and D compounds run in alternation, with an isotope effect calculated for each corresponding H/D pair; error estimates represent the standard error of the mean; average standard error in k is 0.36% and in k_H/k_D 0.30%. ^b The 2D effect is $(0.975)^{2/3} = 0.984$, assuming additivity of the effect of the successive substitutions of deuterium.

Table II. NMR Parameters, α -Carbon of Carboxylic Acids^a

acid	$\delta(^{13}\text{C}_\alpha)$, ppm	$^1\Delta\text{C}_\alpha(n\text{D})$, ppm	$\Delta^1\Delta\text{C}_\alpha(\text{D})$, ppm	$^1J(\text{C},\text{D})$, Hz
acetic- α - <i>d</i> ₃	20.9	0.67	0.22	19.8
acetic- α - <i>d</i> ₂		0.45	0.22	19.8
acetic- α - <i>d</i> ₁		0.23	0.23	19.9
propanoic- α - <i>d</i> ₂	27.4	0.55	0.28	19.6
propanoic- α - <i>d</i> ₁		0.28	0.27	19.7
butanoic- α - <i>d</i> ₂	35.9	0.60	0.30	19.6
butanoic- α - <i>d</i> ₁		0.30	0.30	19.7
pentanoic- α - <i>d</i> ₂	33.8	0.59	0.30	19.6
pentanoic- α - <i>d</i> ₁		0.29	0.29	19.7

^a In CDCl₃, 15.0 MHz, 24 °C; $\delta(^{13}\text{C}_\alpha)$ is the nuclear shielding of the undeuterated acid referenced to internal Me₄Si; estimated precisions are ± 0.03 ppm for nuclear shieldings, ± 0.01 ppm for isotope shifts, and ± 0.1 Hz for coupling constants.

We tried to measure the nuclear shieldings, isotope shifts, and C–D coupling constants at the α -carbon of the NPEs. For the latter two parameters, however, signal-to-noise ratios were poor and the isotope shifts and coupling constants could not be precisely determined. We next focused on the partially α -deuterated parent acids of the NPEs. The ¹H-decoupled ¹³C resonance of the α -carbon of each acid consisted of a well-resolved multiplet representing no isotopic label (singlet), one deuterium (triplet), two deuteriums (pentuplet), and in the case of acetic acid three deuteriums (heptuplet). No undue difficulty was experienced in dissecting these overlapping patterns and measuring the desired parameters.

Table II reports the nuclear shieldings, $\delta(^{13}\text{C}_\alpha)$, for the α -carbons of the isotopically light acids. Maciel and Traficante demonstrated concentration dependent solvent shifts on $\delta(^{13}\text{C}_\alpha)$ of the carbonyl group of acetic acid in several solvents, which reach a minimum in the vicinity of volume fraction 0.040 in CDCl₃.⁵ The spectral data reported here were obtained at nearly constant volume fractions of 0.040 of acid to minimize effects of solvent-induced shifts on the shieldings.

Table II also gives one-bond isotope shifts, $^1\Delta\text{C}_\alpha(n\text{D})$, where n is the number of deuterons attached to α -carbon, obtained upon successive substitution of α -deuterium for α -protium in the C₂–C₇ normal alkanic acids. All $^1\Delta\text{C}_\alpha(n\text{D})$ are upfield with respect to the α -carbon resonances of the undeuterated acids. There is one instance in which our results may be compared with a literature value. Hansen et al.^{1d} report 0.664 ppm for $^1\Delta\text{C}_\alpha(3\text{D})$ of acetic-*d*₃ acid. We obtain 0.67 ± 0.01 ppm.

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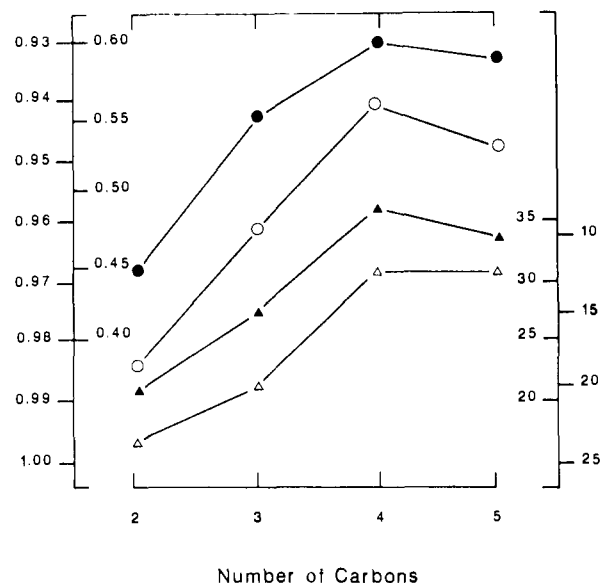


Figure 1. Plots of $^1\Delta\text{C}_\alpha(2\text{D})$ (closed circles, left interior ordinate), β -D KIEs (open circles, left exterior ordinate), $\delta(^{13}\text{C}_\alpha)$ (closed triangles, right interior ordinate), and second-order rate constants for esterolysis of the light isotopomers (open triangles, right exterior coordinate) vs. number of carbons. The NMR parameters are for the C₂–C₃ normal alkanic acids; kinetic isotope effects and rate constants are for esterolysis of the corresponding NPEs.

The $\Delta^1\Delta\text{C}_\alpha(\text{D})$ of Table II are the incremental changes in the isotope shift upon successive substitution of α -deuterium for α -protium. The incremental shifts are additive within the precision of the measurements.

The ¹³C NMR spectra of the α -deuterated acids of Table II yielded the first-order carbon–deuterium coupling constants $^1J(\text{C},\text{D})$.⁶ The reported $^1J(\text{C},\text{D})$ are essentially constant at the level of precision, with a mean value of 19.7 ± 0.1 Hz.

It was of interest to compare trends in the rate constants (light isotopomers) and β -D KIEs for esterolysis to those in $\delta(^{13}\text{C}_\alpha)$ for the isotopically light acids and in $^1\Delta\text{C}_\alpha(2\text{D})$ for the parent acids containing α -CD₂. In Figure 1 the four parameters cited are plotted vs. the number of carbon atoms of the acids. To facilitate the comparison the scales for the different parameters have been adjusted and inverted in the case of the rate constants and β -D KIEs to achieve rough proportionality to ΔG^* and $\Delta\Delta G^*$, respectively. The experimental β -D KIE on the acetate, a “3D” effect, was adjusted to a “2D” effect by assuming additivity of the change in free energy of activation upon successive isotopic substitution, i.e., $(0.975)^{2/3} = 0.984$.

Discussion

It is generally accepted that the β -D KIEs of alkaline ester hydrolysis are predominantly hyperconjugative in origin.^{3,7} The inverse β -D KIEs usually observed in esterolysis of reactive esters with β -C–H(D) bonds by hydroxide and other nucleophiles can be explained by the reduction in hyperconjugation upon activation as the sp² ester carbonyl group rehybridizes to an sp³ tetrahedral-like intermediate during rate-controlling addition of the nucleophile.^{3,7} The trend in the β -D KIEs is therefore toward larger reductions in hyperconjugation upon activation as the chain length of the esters increases.

The NMR of Table II closely follow patterns previously reported for normal alkanes. The decline in $\delta(^{13}\text{C}_\alpha)$ in going from butanoic acid to pentanoic acid corresponds to the γ -gauche effect, which is thought to result from sterically induced hydrogen–hy-

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drogen interactions in hydrocarbon chains of at least four carbons.⁸ The γ -gauche effect is evidence of a conformational dependence of the nuclear shielding; i.e., the hydrocarbon chains of the C₅ acid do not uniquely consist of *all-trans*-zigzag strands, and the observed $\delta(^{13}\text{C}_\alpha)$ is the time-average chemical shift of rapidly interconverting nonequivalent conformers. The isotope shifts may also exhibit the γ -gauche effect. This conclusion is less certain than in the nuclear shieldings because of the experimental errors in the shifts. Nevertheless, the effect definitely exists for one-bond isotope shifts of the normal alkanes as determined at higher resolution.^{1b} Its appearance in the isotope shifts of the carboxylic acids would not be surprising.

The upfield shifts and additivities of the one-bond NMR isotope effects for the acids of Table II are probably due to increases in electron density of C–D bonds compared with C–H bonds.⁹ The C–D bonds are shorter, therefore more shielding, and the isotope shifts are upfield. Two additional lines of experimental evidence obtained here argue against a predominantly hyperconjugative origin for the one-bond isotope shifts. First, with one exception the values of $^1\Delta\text{C}_\alpha(1\text{D})$ for the normal alkanic acids RCDH–CO₂H are identical within experimental error to those determined by Wesener et al.^{1b} for the analogous normal alkanes RCDH–H. The alkanes lack any p-orbital to support hyperconjugation. The exception is the C₂ acid and alkane; we obtain a $^1\Delta\text{C}_\alpha(1\text{D})$ of 0.23 ± 0.01 ppm for acetic acid compared with the reported value^{1b} of 0.187 ppm for ethane. Second, the calculation of the s character at α -carbon from $^1J(\text{C},\text{D})$ values of the C₂–C₅ acids reveals no significant departure from the 25% expected for an sp³ hybrid carbon. In a study of the effects of unsaturation on intrinsic effects in closely related hydrocarbons, Wesener and co-workers^{1b} showed that the degree of s character at carbon is well-correlated with $^1J(\text{C},\text{D})$. The s character, $s(i)$, may be calculated by using the modified Muller–Pritchard relationship (eq 1).¹⁰ The mean $^1J(\text{C},\text{D})$ of 19.7 Hz (Table II) gives an $s(i)$ of 25.7%.

$$s(i) = (6.5144)^{1J(\text{C},\text{D})/500} \quad (1)$$

Figure 1 implies a general parallelism between the activation energies and β -D KIEs of the NPEs, as well as the NMR parameters of the parent acids. A relationship between nuclear shieldings and isotope shifts, which in this instance reflect non-hyperconjugative environmental differences at α -carbon of the ground-state carboxylic acids, has previously been noted¹⁸ and seems indisputable.

A relationship between free energies of activation and β -D KIEs in esterolysis of structurally homologous esters is conceivable. Activation energies reflect free energy differences between ground state(s) and transition state(s); β -D KIEs reflect the hyperconjugation-dependent perturbations of these free energy changes. A causal relationship between the kinetics-related parameters could occur if the activation energy and β -D KIE of an NPE is similarly influenced by ground-state effects, transition-state effects, or both.

An obvious direct conceptual link between the chemical and physical parameters, such as hyperconjugation, is lacking. A tentative candidate for such a link is the ground-state conformation of the esters and corresponding acids, with respect to the average rotameric relationship between the p orbitals of the carbonyl groups and the β -C–H(D) bonds. The conformational dependence of hyperconjugation and its influence on β -D KIEs is well established in solvolysis reactions of rigid molecules that give carbocation-like transition states.^{2,11,12} A maximum β -D KIE (normal effect) is achieved when the developing p orbital of the

carbocation and a β -C–H(D) bond are parallel. In the esterolytic reactions of rotomerically flexible systems such as the open-chain NPEs examined here, a maximum inverse effect ought to be observed when the average overlap of the p orbital of the carbonyl carbon and β -C–H(D) bonds is maximized. The β -D KIE will be affected if certain rotomers of the C₃–C₅ esters are energetically favored. For example, transition-state effects being equal, a trend toward more inverse β -D KIEs with increasing chain length will occur if a population of hyperconjugatively effective rotomers is increased by the greater steric bulk of the larger coiled alkyl chains. NMR shieldings of the methylene carbons of alkanes exhibit conformation-dependent non-hyperconjugative shifts of up to 12 ppm.^{8f} The observed nuclear shift in flexible hydrocarbons, a time-average quantity, depends on the mix of conformers at the conditions of observation. A mutual dependence on ground-state conformation of the hyperconjugative changes in the β -D KIEs of the NPEs and of the non-hyperconjugative changes in nuclear shielding of the acids could produce parallel responses in these two parameters. Small ground-state conformational effects on activation energies of the NPEs and ¹³C NMR one-bond isotope shifts of the acids would finish linking the relationships of Figure 1. Any discussion of a conformational connection between the kinetics-based and NMR parameters is of course completely speculative, since the present data were obtained for different classes of flexible compounds in different solvents. The parallel behaviors of the kinetics-based and NMR parameters are nonetheless intriguing, and they provide the impetus for further work.

Experimental Section

Carboxylic Acids and *p*-Nitrophenyl Esters. Undeuterated *p*-nitrophenyl acetate and butanoate were obtained from Sigma Chemical Co. and used as received. The remaining *p*-nitrophenyl esters were prepared by coupling the appropriate carboxylic acid with *p*-nitrophenol with use of dicyclohexylcarbodiimide in CH₂Cl₂. *p*-Nitrophenyl acetate-*d*₃ was prepared by using >99 atom % acetic-*d*₃ acid obtained from Sigma.

The commercial acetic-*d*₃ acid was too highly deuterated to permit observation of ¹³C NMR isotope shifts for the α -monodeuterated and α -dideuterated species at our conditions. A less highly deuterated acid was prepared by refluxing CH₃CN in 40% NaOH in D₂O, acidifying the solution with concentrated HCl, extracting with CH₂Cl₂, drying (MgSO₄), and distilling. The distilled product was approximately 80 atom % α -deuterated as shown by ¹H NMR.

The α -deuterated versions of the C₃–C₅ normal alkanic acids were prepared by refluxing the appropriate diethyl alkylmalonate or alkylmalonic acid (Aldrich) in a 20% solution of NaOD in D₂O, acidifying the cooled solution with 40% DCl in D₂O, extracting the carboxyl and α -deuterated malonic acid with diethyl ether, and drying the extract (MgSO₄). Distillation of the ethereal residue at atmospheric pressure resulted in the desired decarboxylation to produce the normal alkanic acid deuterated at α -carbon and the carboxyl group. For NMR studies the carboxyl group deuterium was removed by dissolving or suspending the acid in H₂O, acidifying (pH 2), and re-isolating the acid. Each acid was >95% α -dideuterated by ¹H NMR.

Kinetics. Detailed methods for the acquisition of kinetic data and computation of rate constants were as previously described,¹³ except the cell compartment of the spectrophotometer was continuously purged with nitrogen to prevent carbon dioxide absorption by the alkaline solutions.

NMR Spectroscopy. A Jeol FX-60Q Fourier transform NMR spectrometer was used to obtain ¹³C NMR spectra of the acids at 15.0 MHz, using a dual C/H probe, 10-mm sample tubes, and ¹H decoupling. All spectra were obtained in CDCl₃ with internal Me₄Si as the reference. Field stabilization was provided by an external deuterium lock. The temperature was obtained directly in samples equilibrated in the probe with the decoupler activated. Complete ¹³C NMR spectra were obtained by taking 16 384 data points with use of a 4000-Hz spectral width to give a digital resolution of 0.03 ppm. For determination of isotope shifts and C–D coupling constants, a 1000-Hz spectral width and 16 384 data points were used to obtain a digital resolution of 0.12 Hz (8 ppb). The pulse width was 60° and the pulse delay was 3.9 s for all spectra.

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