rhenius activation energy. E_a and $\Delta S^{\pm}$ were 22 kcal mol^{-1} and +1.2 eu for 9-β-D-2′-deoxyribofuranosyladenine and 25 kcal mol^{-1} and +4.4 eu for 9-α-D-2′-deoxyribopyranosyladenine. Bimolecular reactions are characterized by $\Delta S^{\pm}$ values about 20 eu more negative than observed for unimolecular mechanisms.[18,21] Small positive values of $\Delta S^{\pm}$ have been reported for pyrimidine[22] and purine[1] nucleoside as well as for glycopyranoside[18] hydrolysis. Our data are consistent with these observations.

In this, the first systematic study of the effect of sugar structure on the acid-catalyzed hydrolysis of adenine nucleosides, new data are presented which suggest that the variations in hydrolysis rates observed in a homologous series of adenine furanosides can be explained on the basis of the degree of steric interaction between the adenine and the 2′- and/or 3′-hydroxyls. In contrast, the increase in hydrolysis rate of the 2′-, 3′-, or 5′-deoxyfuranoside can be attributed to removal of the electron-withdrawing inductive effect of the hydroxyls. Also identified is a reverse anomeric effect which has not been reported previously for the nucleosides. The reverse solvent isotope effect and the entropies of activation are consistent with the unimolecular mechanism for nucleoside hydrolysis.

Experimental Section

The nucleosides used in this study have been previously identified as to their source and characterization.[23,24] **11** was a gift from Dr. L. B. Townsend of the University of Utah.

The rate of hydrolysis of the adenine nucleosides was followed by using the differential spectrometric method described by Garrett.[4] The rate of change in absorbance at 255 nm was recorded. Pseudo-first-order rate constants (k_1') were determined at HCl concentrations of 0.11, 0.32, 0.62, and 0.89 M at 40 °C. Second-order rate constants, k_2, were determined from the slopes of the plots of k_1' vs. HCl concentration. The rate constants increased with increasing ionic strength; consequently, the ionic strength was maintained at 0.89 by the addition of appropriate amounts of KCl. The temperature dependence of k_1' was determined for β-**2** and **11** in 0.11 M HCl and an ionic strength of 0.89 at temperatures of 25, 40, 49, and 60 °C. The Arrhenius activation energy, E_a, was calculated from the slope of plots of log k_1' vs. $1/T$.

Registry No. 1, 4097-22-7; α-**2**, 3413-66-9; β-**2**, 958-09-8; **3**, 1874-54-0; β-**4**, 6998-75-0; β-**5**, 73-03-0; **6**, 4005-33-8; **7**, 4152-76-5; α-**8**, 3228-71-5; β-**8**, 5536-17-4; **9**, 58-61-7; **10**, 524-69-6; **11**, 17434-50-3.

---

[20] K. J. Laidler, "Chemical Kinetics", 2nd ed., McGraw Hill, New York, 1965, p 89.

[21] F. A. Long and M. A. Paul, *Chem. Rev.*, **57**, 935 (1957).

[22] R. Shapiro and M. Danzig, *Biochemistry*, **11**, 23 (1972).

[23] G. A. LePage and I. G. Junga, *Cancer Res.*, **25**, 46 (1965).

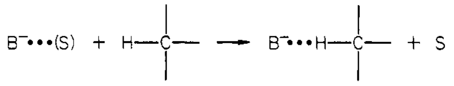
[24] J. L. York and G. A. LePage, *Can. J. Biochem.*, **44**, 331 (1966).

Protonic Charge Densities in Kinetic Acidities of Carbon Acids

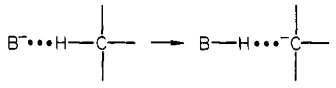
Carl D. Slater[1]

Department of Chemistry, Memphis State University,
Memphis, Tennessee 38152, and Department of Physical
Sciences, Northern Kentucky University, Highland Heights,
Kentucky 41076

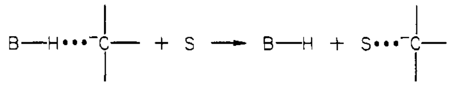
The study of carbon acids has provided fertile ground for the development of chemical theory because proton transfer is one of the simplest chemical reactions for which both rates and equilibrium positions can be measured.[2] In particular, the acidities of nitroalkanes, carbonyl compounds, and fluoroalkanes have been examined intensively. Nitroalkanes have attracted interest because they give anomalous rate–equilibrium correlations based on the Brønsted relationship.[3] Modified Marcus theory[4] has been utilized to interpret this behavior and Agmon has recently argued that under certain conditions kinetic acidities depend largely on the work term in Marcus theory.[5] In this view proton transfer is considered to occur via a three-stage mechanism as outlined in eq 1–3. Step 1 involves the formation of a contact complex in which a solvent molecule in the solvation shell of the base is replaced by the carbon acid. The free-energy change in this stage is referred to as the work term, denoted W_R. It receives its principal contributions from solvent reorganization, steric effects in the reagents, and the difference in hydrogen-bonding strengths in the interactions shown. The second stage of the reaction is the actual proton transfer of eq 2 for which the activation energy is G_a. The specific rate of the forward process is thus given by eq 4, in which Z is the frequency factor.



$$B^-\cdots(S) + H-\overset{|}{\underset{|}{C}}- \longrightarrow B^-\cdots H-\overset{|}{\underset{|}{C}}- + S \quad (1)$$



$$B^-\cdots H-\overset{|}{\underset{|}{C}}- \longrightarrow B-H\cdots{}^-\overset{|}{\underset{|}{C}}- \quad (2)$$



$$B-H\cdots{}^-\overset{|}{\underset{|}{C}}- + S \longrightarrow B-H + S\cdots{}^-\overset{|}{\underset{|}{C}}- \quad (3)$$

$$k = Z\exp[-(W_R + G_a)/RT] \quad (4)$$

For reactions involving a series of structurally similar carbon acids with a common base in the same solvent, steric interactions and solvent reorganization should play a nearly constant role. Accordingly, differences in the strength of hydrogen bonding between the base and the carbon acids should be the predominant variable, and Agmon suggests that in these instances the W_R and G_a terms may vary systematically, leading to abnormal Brønsted α values.

Hydrogen bonding has been the subject of numerous theoretical treatments, and Del Bene has concluded that for hydrogen-bonded species having water or substituted water molecules as proton donors the primary factor responsible for stabilizing the complex is the electrostatic interaction between the proton and the lone pair of electrons from the acceptor.[6] If this finding applies generally to other donor–acceptor combinations, a measure of the abilities of carbon acids to hydrogen bond to a negatively charged base can be developed by considering the acids as charged particles bearing the same charge as the interacting protons. If specific solvent interaction is neglected, the free-energy change associated with bringing two particles of charge Z_A and Z_B from infinite separation to interaction distance d_{AB} in a medium of dielectric constant ϵ is given by eq 5, in which e is the electronic charge.[7]

$$\Delta G_{el} = Z_A Z_B e^2/\epsilon d_{AB} \quad (5)$$

---

[1] Correspondence should be sent to the second address.

[2] An excellent review of this work is given in: Reutov, O. A.; Beletskaya; I. P.; Butin, K. P. "C–H Acids"; Pergamon Press: Oxford, England, 1978.

[3] (a) Bordwell, F. G.; Boyle, W. J., Jr.; Hautala, J. A.; Yee, K. C. *J. Am. Chem. Soc.* **1969**, *91*, 4002. (b) Bordwell, F. G.; Boyle, W. J., Jr.; Yee, K. C. *Ibid.* **1970**, *92*, 5926.

[4] Marcus, R. A. *J. Am. Chem. Soc.* **1969**, *91*, 7224.

[5] Agmon, N. *J. Am. Chem. Soc.* **1980**, *102*, 2164.

[6] Del Bene, J. *J. Am. Chem. Soc.* **1973**, *95*, 5460.

[7] Frost, A. A.; Pearson, R. G. "Kinetics and Mechanism"; John Wiley and Sons, Inc.: New York, 1953; p 133.

0022-3263/81/1946-2173$01.25/0

Table I. Deprotonation of Nitroalkanes by Hydroxide Ion in Water at 25 °C

compd	k_2 (corr)[a]	pK[a]	Z_H[b]
CH_3NO_2	342	10.21	0.0603
$CH_3CH_2NO_2$	118	8.5	0.0386
$CH_3(CH_2)_2NO_2$	98	8.98	0.0388
$CH_3CH(CH_3)NO_2$	16.4	7.68	0.0236
$C_2H_5CH(CH_3)NO_2$	8.8	9.4	0.0248

[a] Data taken from a summary presented in ref 14. Second-order rate constants have been corrected statistically for the number of removable protons. [b] $Z_H = 1 - q_H$, where q_H is the calculated electron density on the acidic proton.

Because other factors are constant, as mentioned above, the complete W_R term is given in eq 6. Substitution into eq 4 leads to eq 7, and because G_a is expected to vary

$$W_R = C + Z_A Z_B e^2/\epsilon d_{AB} \qquad (6)$$

$$\ln k = -C/RT - Z_A Z_B e^2/\epsilon d_{AB} RT - G_a/RT + \ln Z \qquad (7)$$

systematically with $Z_A Z_B e^2/\epsilon d_{AB}$, eq 7 can be rewritten as eq 8, in which K and K' are constants. As seen, in those

$$\ln k = -K Z_A Z_B e^2/\epsilon d_{AB} RT + K' \qquad (8)$$

situations in which d_{AB} remains constant and W_R and G_a vary systematically, ln k should be directly proportional to Z_A, the charge density on the interacting proton. This report establishes such a relationship for two types of carbon acids.

Calculations. Because of the critical dependence of calculated dipole moments on calculated charge densities the agreement between calculated and measured dipole moments appears to offer a good test of how well a particular calculational method handles charge densities. Pople and Gordon[8] have shown that the use of CNDO/2 formalism and parameterization[9] reproduces experimental dipole moments with a high degree of accuracy and for this reason the CNDO/2 method was selected for the present study. The program employed duplicated the results of Segal's QCPE program for a variety of test molecules.[10] Bond angles and distances were those summarized by Pople and Beveridge[11] with the exception that for nitro compounds the ONO angle was taken to be 124° in accord with the measured angle in nitromethane.[12] Calculations were performed on various conformations and the one of best energy is referred to in the correlations. In four instances in the nitro series conformations were found that did not lead to convergence in calculated energies even when the damping technique of Chesnut and Wormer[13] was applied. It is assumed that these are not the conformations of greatest stability. In those instances where two protons of interest on the same carbon atom showed slightly different charge densities as a result of conformational differences, the greater charge density is used because this should be associated with the more acidic proton. The calculated charge densities are summarized in Tables I and II.

Table II. Deprotonation of Fluoroalkanes by Methoxide Ion in Methanol

compd	k (rel)[a]	pK[b]	Z_H[c]
CF_3H	1	31	−0.0074
$(CF_3)_2CFH$	2×10^5	20	0.0627
$(CF_3)_3CH$	1×10^9	11	0.1052

[a] Taken from ref 15. There is an uncertainty of more than an order of magnitude in the relative rate for the bottom compound. [b] Relative to pK for fluorene of ~25. [c] $Z_H = 1 - q_H$, where q_H is the calculated electron density on the acidic proton.

Results and Discussion

Table I shows data[14] for the deprotonation of nitroalkanes by aqueous base at 25 °C and the calculated charge densities for the acidic protons. The second-order rate constants have been corrected for the number of equivalent acidic protons. For comparative purposes, the pK's are also included, revealing the general tendency in this series of greater kinetic acidity being associated with smaller thermodynamic acidity. A plot of log k vs. Z_H gives a least-squares slope of 41.3 log k units/unit Z_H with a correlation coefficient of 0.934. The correlation appears plausible, but because only a range of ca. 1.5 log k units is covered a further test is desirable.

A more stringent test may be offered by the data of Andreades on the kinetics of methoxide ion catalyzed proton exchange in fluoroalkanes.[15] These data, summarized in Table II, cover a relative rate range of 10^9 and a Z_H range of over 0.1. Because the pK's given for these substances are based on kinetic data, the experimental Brønsted α value is not known. Butin et al.[16] reported a slightly different set of pK's based on the reduction potentials for organomercury compounds in dimethylformamide, but it is not clear if these reflect thermodynamic acidities. Nonetheless, the primary requirement for the present purposes appears to have been met in that the kinetic data are for a series of similar acids reacting with a common base in the same solvent. A plot of log k vs. Z_H in this case gives a least-squares slope of 75.5 log k units/unit Z_H and a correlation coefficient of 0.999. Although there is considerable uncertainty in the rate constant for the fastest reaction, a change of even an order of magnitude would not significantly alter the slope of this plot.

A comparison of the slopes of these two plots is also interesting. According to eq 8 the slopes should be inversely proportional to the dielectric constant if a given reaction series were carried out in solvents of different ϵ. While this relationship could not be expected to be maintained strictly for different reaction series in different solvents, it is perhaps worth noting that for the data described above the ratio of the slopes (75.5/41.3 = 1.83) is similar to the reciprocal of the ratio of thd dielectric constants (78.5/32.6 = 2.41) for methanol and water.

On the basis of the rather limited data presented here, it appears that a reasonable correlation exists between protonic charge density and the kinetic acidities of carbon acids when hydrogen bonding in the contact complex plays a major part in determining the activation energy for the overall process of proton removal. Although abnormal Brønsted coefficients may result from a systematic variation in W_R and G_a, the fluoroalkane data tentatively

---

(8) Pople, J. A.; Gordon, M. S. *J. Am. Chem. Soc.* **1967**, *89*, 4253.

(9) Pople, J. A.; Segal, G. A. *J. Chem. Phys.* **1966**, *44*, 3289.

(10) Segal, G. A. Quantum Chemistry Program Exchange, No. 91, Department of Chemistry, University of Indiana, Bloomington, IN 47401.

(11) Pople, J. A.; Beveridge, D. L. "Approximate Molecular Orbital Theory"; McGraw-Hill Book Co.: New York, 1970; pp 111–112.

(12) Brockway, L. O.; Beach, J. Y.; Pauling, L. *J. Am. Chem. Soc.* **1935**, *57*, 2693.

(13) Chesnut, D. B.; Wormer, P. E. S. *Theor. Chim. Acta* **1971**, *20*, 250.

(14) Nielsen, A. T. "The Chemistry of the Nitro and Nitroso Group"; Part 1; Feuer, H., Ed.; Interscience Publishers: New York, 1969; Chapter 7, pp 349–487.

(15) Andreades, S. *J. Am. Chem. Soc.* **1964**, *86*, 2003.

(16) Butin, K. P.; Kashin, A. N.; Beletskaya, I. P.; German, L. S.; Polishchuk, V. R. *J. Organomet. Chem.* **1970**, 25, 11.

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_3NO_2, 75-52-5; $CH_3CH_2NO_2$, 79-24-3; $CH_3(CH_2)_2NO_2$, 108-03-2; $CH_3CH(CH_3)NO_2$, 79-46-9; $C_2H_5CH(CH_3)NO_2$, 600-24-8; CF_3H, 75-46-7; $(CF_3)_2CFH$, 431-89-0; $(CF_3)_3CH$, 382-24-1; hydroxide, 14280-30-9; methoxide, 2143-68-2.

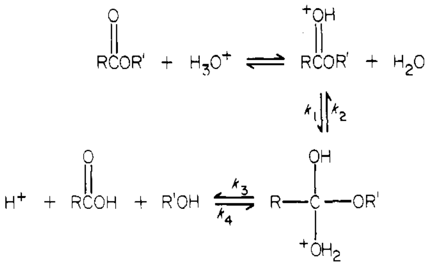
Heavy-Atom Isotope Effects on the Acid-Catalyzed Hydrolysis of Methyl Benzoate[1]

John F. Marlier and Marion H. O'Leary*

Departments of Chemistry and Biochemistry, University of Wisconsin, Madison, Wisconsin 53706

Received December 2, 1980

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 ($k_3 > k_2$).


(1)

$$\mathrm{RC(=O)OR'} + H_3O^+ \rightleftharpoons \mathrm{RC(={}^+OH)OR'} + H_2O \qquad \mathrm{RC(={}^+OH)OR'} \xrightleftharpoons[k_2]{k_1} \mathrm{R{-}C(OH)({}^+OH_2){-}OR'} \qquad H^+ + \mathrm{RC(=O)OH} + \mathrm{R'OH} \xrightleftharpoons[k_4]{k_3} \mathrm{R{-}C(OH)({}^+OH_2){-}OR'} \quad (1)$$

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.

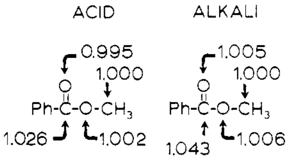


Figure 1. Summary of isotope effects on the acid-catalyzed hydrolysis of methyl benzoate in aqueous solution at 91 °C (this work) and the alkaline hydrolysis of methyl benzoate in aqueous solution at 25 °C (ref 5).

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_2SO_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-

---

(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.

(2) Bender, M. L. *Chem. Rev.* **1960**, *60*, 53. Yates, K. *Acc. Chem. Res.*, **1971**, *4*, 136. Kirby, A. J. *Compr. Chem. Kinet.* **1972**, *10*, 57.

(3) (a) Samuel, D.; Silver, B. *Adv. Phys. Org. Chem.* **1965**, *3*, 129. (b) Bender, M. L. *J. Am. Chem. Soc.* **1951**, *73*, 1626. (c) Sawyer, C. B.; Kirsch, J. F. *Ibid.* **1973**, *95*, 7375.

(4) (a) Fry, A. In "Isotope Effects in Chemical Reactions"; Collins, C. J., Bowman, N. S., Eds.; Van Nostrand Reinhold: New York, 1970; p 364. (b) MacColl, A. *Annu. Rep.—Chem. Soc., Sect. B* **1974**, 71, 77. (c) Dunn, G. E. In "Carbon-13 in Organic Chemistry"; Buncel, E., Lee, C. C., Eds.; Elsevier: Amsterdam, 1977; p 1. (d) Willi, A. V. In "Carbon-13 in Organic Chemistry"; Buncel, E., Lee, C. C., Eds.; Elsevier: Amsterdam, **1977**; p 237. (e) Bigeleisen, J.; Wolfsberg, M. *Adv. Chem. Phys.* **1958**, *1*, 15. (f) Raaen, V. F.; Ropp, G. A.; Raaen, H. P. "Carbon-14"; McGraw-Hill: New York, 1968; p 47. (g) Melander, L.; Saunders, W. H., Jr. "Reaction Rates of Isotopic Molecules"; Wiley: New York, 1980; p 225.

(5) O'Leary, M. H.; Marlier, J. F. *J. Am. Chem. Soc.* **1979**, *101*, 3300.

(6) O'Leary, M. H.; Marlier, J. F. *J. Am. Chem. Soc.* **1978**, *100*, 2582.

(7) Sawyer, C. B.; Kirsch, J. F. *J. Am. Chem. Soc.* **1973**, *95*, 7375.

(8) Ropp, A. G.; Raaen, V. F. *J. Chem. Phys.* **1952**, *20*, 1823.

0022-3263/81/1946-2175$01.25/0