Hydration of Carboxylic Acids and Esters. Evaluation of the Free Energy Change for Addition of Water to Acetic and Formic Acids and Their Methyl Esters

J. Peter Guthrie

Contribution from the Department of Chemistry, University of Western Ontario, London, Ontario, Canada. *Received May 26, 1973*

Abstract: The free energy change when an alcohol (or other organic compound containing a hydroxyl group) reacts with methanol to give a methoxy compound and water is, for compounds with a tetrahedral carbon bearing the hydroxyl, dependent only upon the number of substituents on this carbon and is in all cases small. Extrapolation to ortho esters permits calculation of the free energies of formation, in aqueous solution, of orthoformic ($\Delta G_f^\circ = -136.5$ kcal/mol) and orthoacetic acids ($\Delta G_f^\circ = -139.4$ kcal/mol) and their monomethyl esters ($\Delta G_f^\circ = -121.4$ and -123.6 kcal/mol, respectively). These compounds, which have never been detected, are intermediates in the ^{18}O-exchange reaction of the acids and exchange and hydrolysis reactions of the esters. Knowledge of their free energies of formation permits calculation of the free energy changes for addition of water to the acids or esters and so permits construction of more detailed reaction coordinate diagrams than has previously been possible.

The equilibrium constant for the formation of the tetrahedral intermediate postulated for most acyl group reactions[1] would be of great interest in interpreting mechanistic studies of these reactions but is unknown and probably unmeasurable in many cases. Only in a few very special cases can one detect such an intermediate,[2] and even cases where there is kinetic evidence for its existence are not common.[3,4] Bond energy calculations suggest that such species will indeed be present only in minute amounts at equilibrium.[5] Unfortunately such calculations are only a rough guide, since bond energies are only approximately constant and in any case give an estimate of ΔH in the gas phase, while the desired quantity is ΔG° in solution.

Recently Hine[6,7] has developed and extended the concept of carbon basicity and shown its utility as a tool for understanding and systematizing both equilibrium and kinetic studies of organic compounds. I have found that carbon basicities of alkoxides can serve as a basis for evaluating the equilibrium constants for hydration of acids and esters. The approach used in the present work was one of evaluating the methyl basicities, relative to proton basicities, for a series of alcohols, geminal diols, and hemiacetals. I have found that, within experimental error, these relative methyl basicities[7b] are dependent only upon the degree of substitution at the central carbon atom for the range of compounds of interest here. Then, making the reasonable assumption that this behavior will hold for the corresponding geminal triols (*i.e.*, ortho acids) and their mono- and dimethyl esters, one can calculate free energies of formation in aqueous solution of $RC(OH)_3$ from the free energies of formation of the trimethyl esters. In the course of this work it proved necessary to evaluate the equilibrium constant for hemiacetal formation from acetaldehyde and methanol in aqueous solution, which apparently had not been measured previously, as well as free energies of transfer from the gas phase to aqueous solution for several compounds for which literature values were not available.

Results and Discussion

The methyl basicity of an alkoxide, RO^-, relative to its proton basicity,[6] is measured by the equilibrium constant (or free energy change) for reaction 1.

$$R_1R_2R_3COH + CH_3OH \rightleftharpoons R_1R_2R_3COCH_3 + H_2O \qquad (1)$$

In Table I are found values of the equilibrium constants and standard free energy changes for cases of reaction 1 where R_1, R_2, and R_3 are H, CH_3, OH, or OCH_3. For those cases where reaction 1 corresponds

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[1] (a) S. L. Johnson, *Advan. Phys. Org. Chem.*, **5**, 237 (1967); (b) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1968, pp 463–554; (c) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. 1, W. A. Benjamin, New York, N. Y., 1966, pp 1–211, and references contained therein.

[2] (a) In cyclic or polycyclic systems, tetrahedral intermediates can sometimes be detected[2b] or even isolated.[2c] In noncyclic cases there are only two reports of the detection of tetrahedral intermediates.[2d] (b) D. R. Robinson, *Tetrahedron Lett.*, 5007 (1968); D. R. Robinson, *J. Amer. Chem. Soc.*, **92**, 3138 (1970); J. Hine, D. Ricard, and R. Perz, *J. Org. Chem.*, **38**, 110 (1973); (c) G. Fodor, F. Letourneau, and N. Mandova, *Can. J. Chem.*, **48**, 1465 (1970); A. Stoll, A. Hoffmann, and T. Petrzilka, *Helv. Chim. Acta*, **34**, 1544 (1951); M. M. Shemyakin, V. K. Antonov, A. M. Shkrob, Y. N. Sheinker, and L. B. Senyavina, *Tetrahedron Lett.*, **No. 16**, 701 (1962); R. G. Griot and A. J. Frey, *Tetrahedron*, **19**, 1661 (1963); R. B. Woodward, *Pure Appl. Chem.*, **9**, 49 (1964); H. E. Zaugg, V. Papendick, and R. J. Michaels, *J. Amer. Chem. Soc.*, **86**, 1399 (1964); (d) M. L. Bender, *J. Amer. Chem. Soc.*, **75**, 5986 (1953); S. G. Entelis and O. V. Nesterov, *Dokl. Chem.*, **148**, 174 (1963).

[3] (a) There are a number of reactions for which kinetic evidence has been obtained for the existence of a tetrahedral intermediate in acyl transfer reactions.[1,3b] However, none of these cases is hydrolysis of an ester; the most similar cases are hydrolyses of thiolesters.[3c] (b) W. P. Jencks and K. Salversen, *J. Amer. Chem. Soc.*, **93**, 1419 (1971); T. Okuyama, D. J. Saku, and G. L. Schmir, *ibid.*, **95**, 2345 (1973); T. Maugh and T. C. Bruice, *Chem. Commun.*, 1056 (1969); E. G. Sander, *J. Amer. Chem. Soc.*, **91**, 3629 (1969); G. M. Blackburn, *Chem. Commun.*, 249 (1970); (c) L. R. Fedor and T. C. Bruice, *J. Amer. Chem. Soc.*, **87**, 4138 (1965); R. Hershfield and G. L. Schmir, *ibid.*, **94**, 1263, 6788 (1972).

[4] (a) Numerous studies[1a,4b–d] have demonstrated ^{18}O exchange of the carbonyl oxygen of carboxylic acid derivatives. In only one case[4d] has it been shown that exchange and hydrolysis proceed by the same intermediate. (b) A. J. Kirby, "Comprehensive Chemical Kinetics," Vol. 10, C. H. Bamford and C. F. H. Tipper, Ed., Elsevier, New York, N. Y., 1972, p 165, and references contained therein; (c) C. A. Lane, M. F. Cheung, and G. F. Dorsey, *J. Amer. Chem. Soc.*, **90**, 6492 (1968); (d) M. L. Bender and H. d'A. Heck, *ibid.*, **89**, 1211 (1967).

[5] (a) Using common values[5b] for bond energies and the resonance energy for acetic acid, one can calculate ΔH for the process $RCOOH + H_2O \rightleftarrows RC(OH)_3$ as +26 kcal/mol at 25°; (b) J. D. Roberts and M. C. Caserio, "Basic Principles of Organic Chemistry," W. A. Benjamin, New York, N. Y., 1965.

[6] J. Hine and R. D. Weimar, Jr., *J. Amer. Chem. Soc.*, **87**, 3387 (1965).

[7] (a) J. Hine, *J. Amer. Chem. Soc.*, **93**, 3701 (1971); (b) $K_{HA}{}^{CH_3A}$ in Hine's[6] notation.

Table I. Relative Methyl Basicities[a,b]

R–OH	$\Delta G°$,[b,c] kcal mol^{-1}	R–OH	$\Delta G°$,[b,c] kcal mol^{-1}
(1) CH_3–OH	−0.75	(4) (a) $(CH_3)_3C$–OH	0[d]
(2) (a) CH_3CH_2–OH	−0.07	(b) $(CH_3)_2(OH)C$–OH	+1.11
(b) HO–CH_2–OH	+0.32	(c) $(CH_3)_2(OCH_3)C$–OH	+1.19
(3) (a) $(CH_3)_2CH$–OH	+0.39	Av of 4b–c	+1.2
(b) $(CH_3)(OH)CH$–OH	+0.25	(5) (a) HCO–OH	+0.84
(c) $(CH_3)(OCH_3)CH$–OH	+1.07	(b) CH_3CO–OH	+1.29
Av of 3a–c	+0.6	(c) $(NC_5H_4)(OH)CH$–OH[e]	+0.56
		(d) C_6H_5OH	+0.82[f]

[a] At 25°: the standard state for solutes is an ideal 1 *M* solution with an infinitely dilute reference state; the standard state for the solvent (water) is the pure liquid. [b] For reaction 1, calculated using data given in the Appendix (Table VII). [c] All values are corrected for symmetry effects: ref 6 and S. W. Benson, *J. Amer. Chem. Soc.*, **80**, 5151 (1958). [d] This value is less reliable because of the large error (±1.3 kcal) in $\Delta H_f°(g)$ of $(CH_3)_3COCH_3$ and was not included in the average. [e] Pyridine-4-carboxaldehyde hydrate. [f] Taken from ref 6.

Table II. Equilibrium Constants Evaluated in This Work for Addition to Acids and Esters[a]

Equilibrium[b]	*K*	$\Delta G°$, kcal mol^{-1}
$HCOOH + H_2O \rightleftarrows HC(OH)_3$	2.8×10^{-7}	9.0
$CH_3COOH + H_2O \rightleftarrows CH_3C(OH)_3$	4.0×10^{-9}	12.1
$HCOOCH_3 + H_2O \rightleftarrows HC(OH)_2OCH_3$	4.7×10^{-6}	7.3
$CH_3COOCH_3 + H_2O \rightleftarrows CH_3C(OH)_2OCH_3$	4.0×10^{-9}	12.1
$HCOOCH_3 + OH^- \rightleftarrows HC(OH)(O^-)OCH_3$	7.2×10^{-4}	4.3
$CH_3COOCH_3 + OH^- \rightleftarrows CH_3C(OH)(O^-)OCH_3$	1.4×10^{-7}	10.0

[a] All in aqueous solution, at 25°. [b] Standard state for H_2O is the pure liquid at unit activity; for solutes, the standard state is 1 *M* solution with an infinitely dilute reference state.

Table III. Rate Constants for Hydrolysis of Esters[a]

Reaction	k[b]	$\Delta G^{\ddagger}$, kcal mol^{-1}
$HCOOCH_3 + H_3O^+ \rightarrow$	2.95×10^{-3}	20.8[c]
$HCOOCH_3 + H_2O \rightarrow$	5×10^{-9}	28.8[d]
$HCOOCH_3 + HO^- \rightarrow$	38.4	15.3[e]
$CH_3COOCH_3 + H_3O^+ \rightarrow$	1.03×10^{-4}	22.9[f]
$CH_3COOCH_3 + H_2O \rightarrow$	3.16×10^{-10}	30.4[g]
$CH_3COOCH_3 + HO^- \rightarrow$	1.52×10^{-1}	18.6[h]

[a] All in aqueous solution, at 25°. [b] Dimensions are M^{-1} sec^{-1} except for H_2O reactions which are sec^{-1}. [c] Calculated from the value for ethyl formate in water (footnote *f*) and the ratio of rate constants for methyl and ethyl formates measured in 40% aqueous acetone (N. B. S. Newling and C. N. Hinshelwood, *J. Chem. Soc.*, 1357 (1936)). [d] Estimated from a plot of k_{H_2O} *vs.* σ^* for neutral hydrolysis of methyl esters; k_{H_2O} data from N. J. Cleve and E. K. Euranto, *Suom. Kemistilehti B*, **37**, 126 (1964); W. P. Jencks and J. Carriulo, *J. Amer. Chem. Soc.*, **83**, 1743 (1961), and footnote *g*. [e] H. M. Humphreys and L. P. Hammett, *ibid.*, **78**, 521 (1956). [f] P. Salomaa, L. L. Schaleger, and F. A. Long, *ibid.*, **86**, 1 (1964). [g] Estimated from the value for ethyl acetate (A. Skrabal and A. Zahorka, *Monatsh. Chem.*, **53–54**, 562 (1929)) assuming that the methyl: ethyl rate ratios observed for acid (1.00; footnote *f* and H. Sadek and M. S. A. Elamayem, *Recl. Trav. Chim. Pays-Bas*, **76**, 785 (1957)) and alkaline (1.55; footnote *h* and R. P. Bell and G. M. Waind, *J. Chem. Soc.*, 1979 (1950)) hydrolysis will apply for neutral hydrolysis as well; an average value of 1.28 was used. [h] R. A. Fairclough and C. N. Hinshelwood, *J. Chem. Soc.*, 538 (1937).

to alcohol + methanol giving ether + water, the standard free energy change was calculated from standard free energies of formation in aqueous solution. For cases where reaction 1 represents carbonyl hydrate–hemiacetal or hemiacetal–acetal equilibrium, the ratio of experimental equilibrium constants for reaction with the carbonyl compound was used. The data from which the values in Table I were derived are to be found in the Appendix.

The data in Table I show that there is little change in $\Delta G°$ for reaction 1 even for major changes in structure or pK_a of the hydroxyl compound. Thus it seems reasonable to assume that $\Delta G°$ will be small for any compound with a hydroxyl on carbon. Closer examination of sets 1–4 of the compounds in Table I shows an apparent trend for $\Delta G°$ to be constant if the degree of substitution at the central carbon is the same and to become more positive as the degree of substitution is increased.

Making the assumption that $\Delta G°$ values for reaction 1 when the hydroxy compound is an ortho acid derivative will be the same as the average values for known compounds with the same number of substituents as the central carbon, the standard free energy changes for reactions 2 and 3 can now be calculated.

$$RC(OH)_2OCH_3 + 2CH_3OH \rightleftarrows RC(OCH_3)_3 + 2H_2O \quad (2)$$

$$RC(OH)_3 + 3CH_3OH \rightleftarrows RC(OCH_3)_3 + 3H_2O \quad (3)$$

From the values so obtained and the free energies of formation of the other species (see Appendix) free energies of formation of the ortho acids and their monomethyl esters can be calculated. Finally it is possible to calculate the standard free energy changes for the addition reactions 4 and 5 which are of interest for mechanistic interpretations.

$$RCOOH + H_2O \rightleftarrows RC(OH)_3 \quad (4)$$

$$RCOOCH_3 + H_2O \rightleftarrows RC(OH)_2OCH_3 \quad (5)$$

These values are found in Table II, as well as estimated values for the addition of hydroxide ion[8] to the esters.

Consideration of the scatter of the observed $\Delta G°$ values for reaction 1 about the average values, and the precision of the thermochemical data used in estimating $\Delta G°$ values for reactions 4 and 5, suggests that there is an accumulated uncertainty of *ca.* 2 kcal in these final values. This is larger than would be desired; nevertheless the $\Delta G°$ values calculated here are obtained in a straightforward and thermodynamically reasonable way. The equilibria in question are such that it would be difficult if not impossible to evaluate

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(8) (a) Estimated using pK_a values for the ortho acids and their monomethyl esters calculated from the empirical relationship[8b] between pK_a and σ^* which has been found to hold for alcohols[8b] and aldehyde hydrates;[8c] (b) P. Ballinger and F. A. Long, *J. Amer. Chem. Soc.*, **82**, 795 (1960); (c) G. B. Barlin and D. D. Perrin, *Quart. Rev., Chem. Soc.*, **20**, 75 (1966).

Table IV. Hydrate, Hemiacetal, and Acetal Formation from Acetaldehyde and Aqueous Methanol^{a}

$[CH_3OH]$,^{b} M	$[H_2O]$,^{c} M	R^{d}	F^{e}	$[CH_3OH]/[H_2O]$
0	55.5	0.870		
0.328	3.5	1.02	0.47	0.00599
0.635	2.9	1.17	0.50	0.0120
1.22	1.7	1.49	0.54	0.0236
2.12	49.8	1.98	0.55	0.0423
3.48	47.0	2.84	0.60	0.0741
10.02	33.6	9.14	0.86	0.298

^{a} At 32.5°, with 0.001 M HCl. ^{b} Calculated from the weight of methanol present in 10 ml of solution. ^{c} Calculated assuming the density of the solution is the same as for methanol–water mixtures of the same methanol content. ^{d} R = ratio of total integral for hydrate, hemiacetal, and acetal to integral for free aldehyde; see text. ^{e} $F = (R - K_1[H_2O])/[CH_3OH]$; see text.

Table V. Thermochemical Data^{a}

Compd	$\Delta H_f°$(g), mol^{-1}	$S°$(g), cal mol^{-1} deg^{-1}	$\Delta G_f°$(g), kcal mol^{-1}	$\Delta G_f°$(aq), kcal mol^{-1}
(a) Experimental Values Used in This Work				
H_2O	-57.80^{b}	45.11^{b}	-54.64^{b}	$-56.69^{b,c}$
HCOOH	-90.49^{d}	59.45^{d}	-83.89^{d}	-88.83^{e}
CH_3OH	-48.08^{b}	56.8^{b}	-38.69^{b}	-41.88^{e}
CH_3COOH	-103.26^{f}	67.52^{d}	-89.36^{h}	-94.21^{e}
$HCOOCH_3$	-83.60^{d}	72.0^{d}	-71.03^{d}	-72.01^{e}
CH_3CH_2OH	-56.24^{b}	67.4^{b}	-40.30^{b}	-43.31^{e}
CH_3OCH_3	-43.99^{d}	63.83^{d}	-26.99^{d}	-27.00^{e}
$CH_3CH_2OCH_3$	-51.73^{d}	74.24^{d}	-28.12^{d}	-28.16^{e}
CH_3COOCH_3	-97.9^{d}	76.45^{g}	-77.0^{h}	-78.4^{e}
$(CH_3)_2CHOH$	-65.12^{d}	74.07^{d}	-41.49^{d}	-44.55^{e}
$(CH_3)_2CHOCH_3$	-60.24^{d}	80.86^{d}	-28.89^{d}	-28.94^{e}
$(CH_3)_3COH$	-74.72^{f}	77.98^{d}	-42.51^{h}	-45.09^{e}
$HC(OCH_3)_3$	-128.41^{i}	94.57^{g}	-86.53^{h}	-89.05^{e}
$(CH_3)_3COCH_3$	$-70^{d,j}$	84.36^{d}	-30^{d}	-30^{e}
$CH_3C(OCH_3)_3$	-137.14^{g}	99.70^{g}	-87.08^{h}	-89.56^{e}
(b) Values Calculated in This Work^{g}				
$HC(OH)_3$				-136.5
$CH_3C(OH)_3$				-138.8
$HC(OH)_2OCH_3$				-121.4
$CH_3C(OH)_2OCH_3$				-123.0

^{a} At 25°; standard states are hypothetical ideal gas at 1 atm and 1 M solution with an infinitely dilute reference state, unless otherwise stated. ^{b} F. D. Rossini, D. D. Nagman, W. H. Evans, S. Levine, and I. Jaffe, "Selected Values of Chemical Thermodynamic Properties," National Bureau of Standards Circular No. 500, U. S. Government Printing Office, Washington, D. C., 1952. ^{c} Standard state is pure liquid at unit activity. ^{d} D. R. Stull, E. F. Westrum, Jr., and G. C. Sinke, "The Chemical Thermodynamics of Organic Compounds," Wiley, New York, N. Y., 1967. ^{e} Calculated from $\Delta G_f°$(g) using ΔG_t values from Table VI. ^{f} J. D. Cox and G. Pilcher, "Thermochemistry of Organic and Organometallic Compounds," Academic Press, New York, N. Y., 1970. ^{g} See text. ^{h} Calculated using the $\Delta H_f°$ and $S°$ values shown. ^{i} Reference 11. ^{j} $\Delta H_f°$(g) = 70.0 ± 1.3 kcal: E. J. Smutny and A. Bondi, *J. Phys. Chem.*, **65**, 546 (1961).

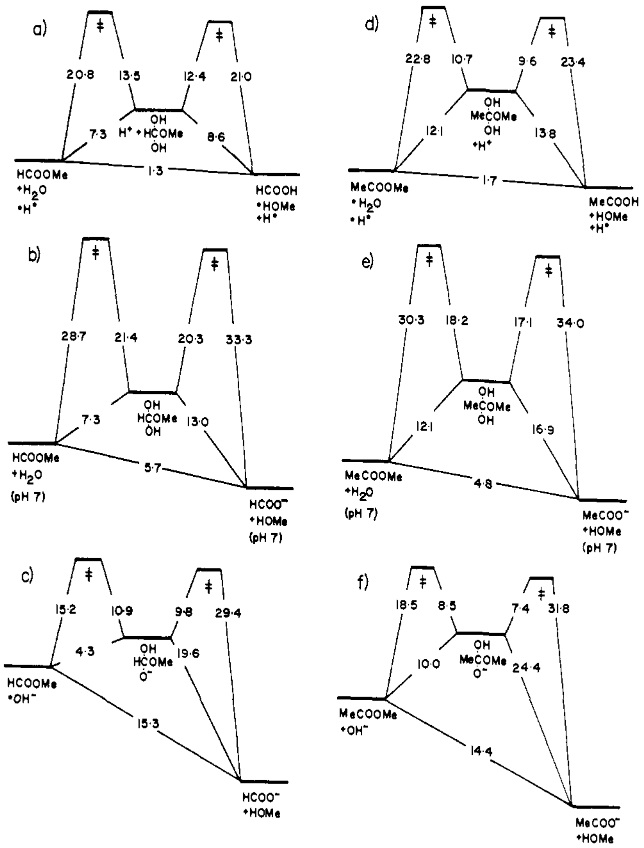

Figure 1. Reaction coordinate diagrams for acid-catalyzed, uncatalyzed, and hydroxide-catalyzed hydrolysis of methyl formate and methyl acetate. Free energies of formation of the tetrahedral intermediates were evaluated in this investigation. Free energies of activation for the individual steps were calculated as described in the text. The diagrams for the uncatalyzed reactions are calculated for pH 7, even though the hydroxide ion catalyzed path would predominate at this pH (the uncatalyzed path makes the largest contribution at *ca.* pH 5).

the equilibrium constants directly. It is of interest to compare these $\Delta G°$ values for formation of the tetrahedral intermediate with $\Delta G^{\ddagger}$ values for hydrolysis reactions of the esters; available values are summarized in Table III. In all cases the $\Delta G^{\ddagger}$ values are larger than the corresponding $\Delta G°$ values, showing that the $\Delta G°$ values are not unreasonable. However, for both acid- and base-catalyzed hydrolyses, the value of $\Delta G^{\ddagger}$ for reversion of the tetrahedral intermediate to ester and water[9] is *ca.* 9–12 kcal/mol, corresponding to a rate constant of *ca.* 10^6–10^4 sec^{-1}; thus the tetrahedral species is a very short-lived intermediate. In Figure 1 are shown reaction coordinate diagrams for these reactions, drawn for 1 M H$^+$, pH 7, and 1 M OH$^-$. Since ^{18}O-exchange experiments have not been done for either of the esters considered here, it is necessary to assume that k_h/k_e will be similar to the values for the esters which have been studied[4b–d,10] (methyl and ethyl benzoate, acetate, and trifluoroacetate). These values, for acid, water, and hydroxide reactions, are all in the range 2.0–27.7. Thus, an assumed value of 13 for k_h/k_e should be acceptably close to the true values for methyl acetate and formate. Making this assumption, Figure 1 was constructed. Although one must bear in mind the uncertainty in the free energy level of the intermediate, these diagrams give a more detailed picture of the

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[9] The transition state for the reversion reaction must have the same composition as that for the formation of the tetrahedral intermediate; for the acid-catalyzed process ester + water + H$^+$, and for the base-catalyzed process ester + water − H$^+$. For the acid-catalyzed hydrolysis, the tetrahedral intermediate is almost certainly too weakly basic to be protonated to any significant extent in 1 M H$^+$; thus the reversion reaction will be a second-order acid-catalyzed process; $\Delta G^{\ddagger}$ is calculated for the pseudo-first-order rate constant at 1 M H$^+$. For the base-catalyzed hydrolysis the tetrahedral intermediate is sufficiently acidic[8] to be essentially completely ionized in 1 M OH$^-$; thus the reversion reaction will be first order.

[10] S. A. Shain and J. F. Kirsch, *J. Amer. Chem. Soc.*, 90, 5848 (1968).

Table VI. Free Energies of Transfer at 25° from the Ideal Gas State to 1 *M* Aqueous Solution

Compd	*C*,[a] *M*	*P*,[b] mm	$\Delta G_t°$, kcal mol^{-1}
HCOOH			−4.94[c]
CH_3OH	1.09[d]	3.85[d]	−3.19
CH_3COOH			−4.85[c]
$HCOOCH_3$	3.89[e]	571[f]	−0.98
CH_3CH_2OH	1.33[d]	6.3[d]	−3.01
CH_3OCH_3	0.99[d]	760[d]	−0.01
$C_2H_5OC_2H_5$	0.80[d]	537[d]	−0.07
$C_2H_5OCH_3$			−0.04[g]
CH_3COOCH_3			−1.38[i]
$(CH_3)_2CHOH$	0.352[d]	1.55[d]	−3.06
$(CH_3)_2CHOCH_3$	0.91[h]	635[d]	−0.05
$(CH_3)_3COH$			−2.58[i]
$HC(OCH_3)_3$	3.24[j]	35.4[f]	−2.52
$(CH_3)_3COCH_3$	0.55[k]	245[f]	−0.32
$CH_3C(OCH_3)_3$	2.04[j]	24[f,l]	−2.48

[a] Concentration of compound in aqueous solution. [b] Equilibrium vapor pressure of compound for an aqueous solution of concentration *C*. [c] Calculated using values for the free energy of transfer from liquid to 1 *M* aqueous solution from W. A. Kaye and G. S. Parks, *J. Chem. Phys.*, **2**, 141 (1934), and $\Delta G_f°$ values for liquid and monomeric gas from D. R. Stull, E. F. Westrum, Jr., and G. C. Sinke, "The Chemical Thermodynamics of Organic Compounds," Wiley, New York, N. Y., 1967. [d] Reference 6. [e] Saturated solution: "Handbook of Chemistry and Physics," 37th ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1955. [f] Vapor pressure of the pure liquid. [g] Estimated from the values for dimethyl and diethyl ethers, assuming that ΔG_t for methyl ethyl ether will be midway between these two. [h] Saturated solution: J. C. Krantz, Jr., C. J. Carr, W. E. Evans, Jr., and R. Musser, *J. Pharmacol.*, **87**, 132 (1946); *Chem. Abstr.*, **40**, 5144 (1946). [i] Calculated from results in J. A. V. Butler, C. M. Ramchandani, and D. W. Thomson, *J. Chem. Soc.*, 280 (1935). [j] Saturated solution: this work. [k] Saturated solution: J. W. McBain and P. H. Richards, *Ind. Eng. Chem.*, **38**, 642 (1946). [l] Estimated from the normal boiling point using the Clausius–Clapeyron equation and a value for ΔH_v estimated after I. Wadsö, *Acta Chem. Scand.*, **20**, 544 (1960).

Table VII. Equilibrium Constants Used in Evaluating the Relative Methyl Basicities in Table I[a]

Reaction	*K*	$\Delta G°$, kcal mol^{-1}
$CH_2O + H_2O \rightleftarrows CH_2(OH)_2$	2.28×10^3 [b]	−4.57
$CH_2O + CH_3OH \rightleftarrows CH_2(OH)OCH_3$	$1.3 \times 10^3\ M^{-1}$ [b]	−4.25
$CH_3CHO + H_2O \rightleftarrows CH_3CH(OH)_2$	1.06[c]	−0.03
	1.07[d,e]	−0.04
$CH_3CHO + CH_3OH \rightleftarrows CH_3CH(OH)OCH_3$	$0.70\ M^{-1}$ [d,e]	+0.21
$CH_3CHO + 2CH_3OH \rightleftarrows CH_3CH(OCH_3)_2 + H_2O$	$0.0285\ M^{-2}$ [f–h]	+2.12
	$0.029\ M^{-2}$ [d,e]	+2.10
$(CH_3)_2CO + H_2O \rightleftarrows (CH_3)_2C(OH)_2$	1.4×10^{-3} [e,i]	+3.90
$(CH_3)_2CO + CH_3OH \rightleftarrows (CH_3)_2C(OH)OCH_3$	$2.2 \times 10^{-4}\ M^{-1}$ [e,g,i]	+5.01
$(CH_3)_2CO + 2CH_3OH \rightleftarrows (CH_3)_2C(OCH_3)_2 + H_2O$	$7.2 \times 10^{-6}\ M^{-2}$ [g,j]	+7.02
$CH_3COOH + CH_3OH \rightleftarrows CH_3COOCH_3 + H_2O$	$0.0571\ M^{-1}$ [k]	+1.70
$ArCHO + H_2O \rightleftarrows ArCH(OH)_2$	1.28[b,l]	−0.15
$ArCHO + CH_3OH \rightleftarrows ArCH(OH)OCH_3$	$0.50\ M^{-1}$ [b,l]	+0.41
$HCOOH + CH_3OH \leftrightarrows HCOOCH_3 + H_2O$	$0.122\ M^{-1}$ [m]	+1.25

[a] For reactions where water is reactant or product, the equilibrium constant is defined for activity of liquid water = 1; all reactions studied in water as solvent unless otherwise specified; temperature = 25°. [b] E. G. Sander and W. P. Jencks, *J. Amer. Chem. Soc.*, **90**, 6154 (1968). [c] J. L. Kurz, *ibid.*, **89**, 3524 (1967). [d] This work. [e] Corrected to 25° as described in ref 7; for the addition of water to acetaldehyde the $\Delta S°$ value from footnote *c* was used. [f] H. Adkins and E. W. Adams, *J. Amer. Chem. Soc.*, **47**, 1368 (1925). [g] In methanol as solvent; these equilibrium constants are assumed to be the same in water as solvent. [h] Corrected for hemiacetal formation, since the analytical method used in footnote *f* would not distinguish between aldehyde and hemiacetal. [i] J. Hine and R. W. Redding, *J. Org. Chem.*, **35**, 2769 (1970). [j] J. M. Bell, D. G. Kubler, P. Sartwell, and R. G. Zepp, *ibid.*, **30**, 4284 (1965). [k] A. R. Fersht and W. P. Jencks, *J. Amer. Chem. Soc.*, **92**, 5442 (1970). [l] Ar is 4-pyridyl. [m] A. R. Fersht, *J. Amer. Chem. Soc.*, **93**, 3504 (1971).

energetics of the ester hydrolysis reaction than has heretofore been possible.

In summary, from the free energies of formation of ortho esters and esters in the gas phase, and their free energies of transfer to aqueous solution, one can calculate the free energy of hydration of the ester. The methods used in this paper are obviously quite general and could be applied to a great many reactions of current interest. The major limitation to widespread use of this approach is the dearth of thermochemical data for carbonyl and carboxyl derivatives and of activity coefficient data for small water soluble compounds.

Experimental Section

Acetaldehyde (BDH reagent grade) was freshly distilled immediately before use. Trimethyl orthoformate (Aldrich, bp 100.2°) and trimethyl orthoacetate (Eastman, bp 110°) were freshly distilled and center cuts of the indicated boiling points were used. Inorganic chemicals were reagent grade. Nmr spectra were recorded on Varian T60 or HA 100 spectrometers.

Solubilities were measured by shaking the organic liquid with 0.01 *M* phosphate buffer, pH 7 (trimethyl orthoformate), or 0.01 *N* sodium hydroxide (trimethyl orthoacetate) in a glass-stoppered tube and allowing the system to come to equilibrium, with frequent shaking, in a water bath at 25.0 ± 0.1°. When the layers had separated, a sample of the lower phase was placed in an nmr tube, and after taking the nmr spectrum to confirm that no hydrolysis had occurred, concentrations were evaluated by integration.

Hemiacetal Formation. A solution *ca.* 1 *M* in acetaldehyde was prepared in water. A 5-ml portion of this solution was added to a 10-ml volumetric flask containing a weighed amount of methanol and enough water to give almost 5 ml of liquid. Then 100 μl of 0.1 *N* HCl was added and the flasks were made up to the mark with water. Samples of these solutions were used for nmr spectra (recorded on a Varian HA 100 instrument, *ca.* 24–48 hr after preparation; the ratio of integrals was unchanged after an hour in the probe). The ratio, *R*, of the total peaks at *ca.* δ 1 (CH_3-C(OR)$_2$H) to total peaks at *ca.* δ 2 (CH_3-CHO) was evaluated from the integrals (see Table IV). It may be shown that the ratio, *R*, is given by

$$R = K_1[H_2O] + K_2[CH_3OH] + K_3[CH_3RH]^2/[H_2O]$$

where K_1 is the equilibrium constant for addition of water, K_2 is the equilibrium constant for hemiacetal formation, and K_3 is the equilibrium constant for acetal formation (all with dimensions of M^{-1}; note that the concentration of water is here expressed in units of molarity). When $[CH_3OH] = 0$, K_1 can be evaluated; then one can write

$$F = (R - K_1[H_2O])/[CH_3RH] = K_2 + K_3([CH_3OH]/[H_2O])$$

A graph of *F vs.* ($[CH_3OH]/[H_2O]$) gives K_2 as the intercept and K_3 as the slope. In this way were obtained $K_1 = 0.016\ M^{-1}$, $K_2 = 0.50\ M^{-1}$, and $K_3 = 1.2\ M^{-1}$ at 32.5°; correcting to 25° after Hine[7] one obtains $K_1 = 0.020\ M^{-1}$, $K_2 = 0.70\ M^{-1}$, and $K_3 = 1.6\ M^{-1}$ at 25°. Values for K_1 and K_3 are in good agreement with literature values; see Table VII.

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Appendix

$\Delta H_f°$(g) has been measured for trimethyl orthoformate;[11] for trimethyl orthoacetate, $\Delta H_f°$(g) was calculated using the bond–bond interaction scheme of Pihlaja.[12] The standard entropies of the gaseous ortho esters were estimated using the standard entropies of the corresponding hydrocarbons and the correction factor proposed by Stull, *et al.*[13] (it was assumed that this factor should be applied for each oxygen[14]). $S°$(g) for methyl acetate was estimated from the value of $S°$(g) for ethyl acetate,[13] using the difference in $S°$(g) for ethanol and methanol[13] ($\Delta S° = 10.25$).

In Table V are collected the thermochemical data used in this paper, as well as the free energies of formation in aqueous solution estimated for ortho acid derivatives. To calculate $\Delta G_f°$(aq) values it was necessary to evaluate free energies of transfer, ΔG_t, from standard state (g, 1 atm) to standard state (aq, 1 *M*); the data used to evaluate ΔG_t are found in Table VI.

Most of the relative methyl basicities found in Table I are calculated from equilibrium constants for reaction of carbonyl compounds; the equilibria which were used are found in Table VII.

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(11) K. Pihlaja and M.-L. Tuomi, *Acta Chem. Scand.*, **25**, 465 (1971).

(12) K. Pihlaja, *Acta Chem. Scand.*, **25**, 451 (1971).

(13) D. R. Stull, E. F. Westrum, Jr., and G. C. Sinke, "The Chemical Thermodynamics of Organic Compounds," Wiley, New York, N. Y., 1969.

(14) No standard entropy data are available for any ortho ester; the only acetal for which $S°$(g) is available is dimethoxymethane[12] for which $S°$(g) estimated as described is within 0.6 eu of the observed value.

The Solvent System Ethanol–2,2,2-Trifluoroethanol as a Medium for Solvolytic Displacement

Daniel A. da Roza, L. J. Andrews,* and R. M. Keefer

Contribution from the Department of Chemistry, University of California, Davis, California 95616. *Received February 7, 1973*

Abstract: A comparative rate study of the solvolyses of benzyl bromide and chloride and their *m*-fluoro and *p*-methyl derivatives in various mixtures of ethanol and 2,2,2-trifluoroethanol has been conducted. The reactivity of *p*-methylbenzyl chloride increases and that of *m*-fluorobenzyl chloride decreases with increasing trifluoroethanol content of the medium; benzyl chloride is relatively insensitive to changes in solvent composition. These reactivity differences reflect the electronic influence of substrate ring substituents on the extent to which solvent is involved as a nucleophile and as an electrophile in rate-determining processes. These differences are also reflected in the influences of changes in solvent composition on the composition of reaction product (ethyl ether *vs.* trifluoroethyl ether) as the ring substituents of the reacting halides are changed. The reactivity ratios of the substituted benzyl bromides and the corresponding benzyl chlorides are insensitive to changes in ring substituents when ethanol is the medium but increase significantly with increasing trifluoroethanol content of the medium. The variations in the observed solvent influence on bromide–chloride reactivity ratios are ascribed to differences in disposition of the bromides and chlorides to solvolyze by processes which are subject to internal return.

In accounting for the response of substrate reactivity to change in the medium, eq 1, as formulated by

$$\mathrm{d}\log k = \left(\frac{\partial \log k}{\partial Y}\right)_N \mathrm{d}Y + \left(\frac{\partial \log k}{\partial N}\right)_Y \mathrm{d}N \qquad (1)$$

Winstein, Grunwald, and Jones,[1] is frequently applied. This equation relates variations in solvolysis rate constant (k) to variations in ionizing power (Y) and nucleophilic character (N) of the solvent. The term $(\partial \log k/\partial Y)_N$ has been equated with the Grunwald–Winstein[2] m value (eq 2), as measured by the slope of a plot of

$$\log k = mY + \log k_0 \qquad (2)$$

values of log k *vs.* Y for reactions in media which are comparable in nucleophilicity but variable in ionizing power, *e.g.*, ethanol–water mixtures.

The Y value of a solvent is defined as the logarithm of the solvolysis rate ratio for reaction of *tert*-butyl chloride in that solvent and in 80% aqueous ethanol, and k_0 is the rate constant for reaction of the substrate in 80% aqueous ethanol. Substrates which have m values close to that for *tert*-butyl chloride (unity) are considered as prone to solvolyze by processes in which there is a high degree of bond breaking and correspondingly extensive involvement of the solvent as an electrophile, at the transition state. As their m values diminish, the substrates presumably become increasingly sensitive to changes in solvent nucleophilicity.

The components of the binary mixtures generally used in connection with the Grunwald–Winstein correlation differ significantly in dielectric constant as well as in their capacities to solvate the departing anion, *e.g.*, halide ion in alkyl halide solvolysis. The dielectric constant of the medium is thus built into the Y value. Therefore the m value reflects the sensitivity of substrate reactivity to changes in the dielectric constant of the solvent as well as in its electrophilic character.

In the current investigation, consideration has been given to the means of eliminating the dielectric constant as a variable in assessing the influence of medium changes as reflected in solvolysis rate. Experimental attention has focused on the solvent system ethanol–

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(2) E. Grunwald and S. Winstein, *ibid.*, **70**, 846 (1948).