

lines in a simple phantom by Lauterbur,⁵⁴ who subsequently obtained images, by the projection-reconstruction method, of ³¹P nuclei in particular metabolites.⁵⁵ The ³¹P chemical shifts are an order of magnitude larger than proton chemical shifts so that the field gradients may more easily be applied without obliterating the spectral structure. It is clearly important in such applications to work in the highest possible magnetic field in order to open up the chemically shifted spectra.

We should note in passing the complementary nature of such work to "topical" NMR spectroscopy⁵⁶ in which high-resolution NMR spectra of ³¹P and other nuclei are obtained from well-defined small volumes in the human body using auxiliary magnet coils.

Other potential applications of NMR imaging include

(54) Lauterbur, P. C.; Kramer, D. M.; House, W. V.; Chen, C. N. *J. Am. Chem. Soc.* **1975**, *97*, 6866.

(55) Bendel, P.; Lai, C.-M.; Lauterbur, P. C. *J. Magn. Reson.* **1980**, *38*, 343.

(56) Gordon, R. E. *Phys. Bull.* **1981**, *32*, 178.

the investigation of fluid flow,⁵⁷ the development of NMR microscopy for NMR imaging of small objects both animate and inanimate,⁵⁸ the nondestructive examination of the interior of food products, the diffusion of water in soil and in building materials,⁵⁹ and the imaging and interior examination of solid materials in conjunction with high-resolution solid-state NMR line-narrowing procedures.⁶⁰

Finally we may note that the ideas of NMR imaging may be extended to the imaging of unpaired electrons using electron spin resonance (ESR). Such extension has been applied to the study of the distribution of defects in diamonds⁶¹ and of free radicals in solids.⁶²

(57) Garroway, A. N. *J. Phys. D* **1974**, *7*, L159.

(58) Mansfield, P.; Grannell, P. K. *Phys. Rev. B: Solid State* **1975**, *12*, 3618.

(59) Gummerson, R. J.; Hall, C.; et al. *Nature (London)* **1979**, *281*, 56.

(60) Richards, R. E.; Packer, K. J. "Nuclear Magnetic Resonance Spectroscopy in Solids"; The Royal Society: London, 1981.

(61) Hoch, M. J. R.; Day, A. R. *Solid State Commun* **1979**, *30*, 211.

(62) Hoch, M. J. R. *J. Phys. C* **1981**, *14*, 5659.

(63) Smith, F. W. *Lancet* **1982**, Apr 24, 974.

Thermodynamics of Metastable Intermediates in Solution

J. PETER GUTHRIE¹

Department of Chemistry, University of Western Ontario, London, Canada, N6A 5B7

Received March 5, 1982 (Revised Manuscript Received October 4, 1982)

Chemical reactions frequently involve short-lived intermediates that are never present at detectable concentrations, yet are obligatory stages on the path from starting materials to products. There is as yet no general procedure for determining the free energy level of such an intermediate relative to the starting materials. This situation should be contrasted with that for starting materials and products or for intermediates which accumulate to detectable levels, where there are numerous methods for determining the relative free energy levels. If all else fails it will always be possible, for isolable starting materials and products, to determine the appropriate thermodynamic quantities (heat of formation, standard entropy, and so the free energy of formation) to permit calculation of the free energy change for the reaction.

The lack of a suitable method for intermediates that are too unstable to accumulate to detectable levels has been a serious nuisance, since such intermediates occur in most of the important reactions in organic chemistry. Such species are found in acyl-transfer reactions (tetrahedral intermediates), reactions α to carbonyl groups

(enols), and phosphoryl-transfer reactions (penta-coordinate intermediates). For all such reactions involving simple substrates, the intermediates are detectable only under very special circumstances.

We have been engaged for several years²⁻¹⁴ in developing methods that will provide at least a partial solution to this problem and believe that we now have developed a satisfactory general approach that permits the evaluation of the free energy level of any intermediate whose instability derives from the presence of a hydroxyl group but whose analogue with an alkoxyl group is stable. Thus far we have concentrated on reactions in aqueous solution, but in principle there is no reason why the method cannot be extended to other solvents. This includes a large fraction of the meta-

(1) E. W. R. Steacie Fellow, 1980-1982.

(2) Guthrie, J. P. *J. Am. Chem. Soc.* **1973**, *95*, 6999.

(3) Guthrie, J. P. *J. Am. Chem. Soc.* **1974**, *96*, 3608.

(4) Guthrie, J. P. *Can. J. Chem.* **1975**, *53*, 898.

(5) Guthrie, J. P. *Can. J. Chem.* **1976**, *54*, 202.

(6) Guthrie, J. P. *J. Am. Chem. Soc.* **1977**, *99*, 3991.

(7) Guthrie, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 5892.

(8) Guthrie, J. P. *Can. J. Chem.* **1977**, *55*, 3562.

(9) Guthrie, J. P. *Can. J. Chem.* **1978**, *56*, 962.

(10) Guthrie, J. P. *Can. J. Chem.* **1978**, *56*, 2342.

(11) Guthrie, J. P. *Can. J. Chem.* **1979**, *57*, 236.

(12) Guthrie, J. P.; Cullimore, P. A. *Can. J. Chem.* **1979**, *57*, 240.

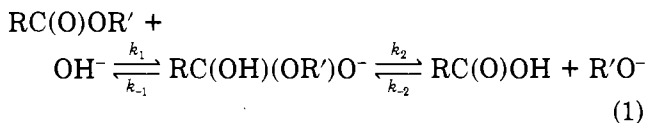
(13) Guthrie, J. P. *Can. J. Chem.* **1979**, *57*, 454.

(14) Guthrie, J. P.; Cullimore, P. A. *Can. J. Chem.* **1980**, *58*, 1281.

J. Peter Guthrie was born in Port Elgin, Ontario, Canada, in 1942. He received his undergraduate education at the University of Western Ontario and his Ph.D. from Harvard University in 1968. After a year as a NRC of Canada postdoctoral fellow at Princeton University he joined the faculty at the University of Western Ontario, where he is now Professor of Chemistry.

stable intermediates of organic chemistry as well as a number of species normally classified as inorganic.

In the mechanistic analysis of a chemical reaction, a method for determining free energy level of an intermediate is of considerable value. The free energy level of the intermediate will frequently provide the final piece of information required for a complete solution of the kinetics of reaction; this can be illustrated for the case of ester hydrolysis:¹⁵



The directly accessible quantities are the overall rate of reaction, $k_{\text{obsd}} = k_1 k_2 / (k_{-1} + k_2)$; the overall equilibrium constant, $K_{\text{eq}} = k_1 k_2 / k_{-1} k_{-2}$; and the partitioning ratio for the intermediate (normally measured by an isotope-exchange experiment), $r = k_{-1} / k_2$. Although these three quantities are insufficient for a complete specification of the system, the determination of a fourth independent quantity, the equilibrium constant for formation of the tetrahedral intermediate, $K_{\text{add}} = k_1 / k_{-1}$, permits the evaluation of all four rate constants required to give a complete description of the system. These in turn permit the actual microscopic rate constants for breakdown of the intermediate to be discussed and the energetics of each stage of the reaction to be analyzed.

Method

Our method is based upon the observation that the equilibrium constant for reaction 2 should be very close



to unity for all examples. Indeed if the bond energy approximation were strictly valid, the free energy change would be zero for all examples of the reaction, because the number of C–O and O–H bonds is the same in starting materials and products, and there is no change in the number of molecules. It is immediately apparent that symmetry corrections¹⁶ will be necessary when more than one OR or OH group is present, and also that steric corrections will be needed when the substituents on the central carbon are bulky enough to interfere with the R group in OR, since this effect will be more important for OR than for OH. So long as these steric corrections are not large, it seems possible to estimate them adequately by simple procedures such as those recommended by Pihlaja.¹⁷

When we first devised this approach, it seemed that the free energy change depended only upon the number of substituents on the central carbon.² On further examination it became clear that there was a small but significant dependence upon the electron-withdrawing properties of the substituents on the central carbon.¹ This was best shown by plotting the free energy change for reaction 2 (corrected for both steric and symmetry

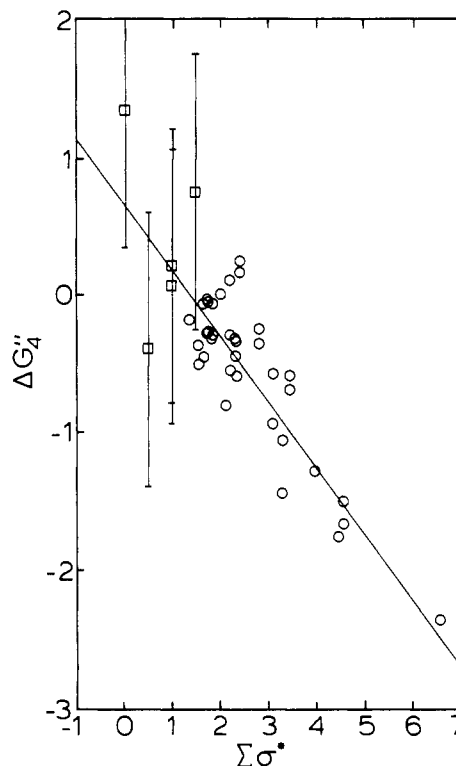


Figure 1. Graph of ΔG_4° vs. $\sum \sigma^*$ for the reaction $\text{C-OR} + \text{H}_2\text{O} = \text{C-OH} + \text{HOR}$. The symbols with error bars are for points based upon free energy of formation data and are for "hydrolyses" of simple ethers and of acetals of formaldehyde. The circles are based on equilibrium data, i.e., ratios of equilibrium constants for hemiacetal and hydrate formation or acetal and hemiacetal formation. The line was determined by weighted least squares.

effects) against the sum of the σ^* values for the substituents. Such a plot gave a linear correlation, eq 3,

$$\Delta G'' = (0.66 \pm 0.12) - (0.48 \pm 0.04) \sum \sigma^* \quad (3)$$

with a slope corresponding to a ρ^* value of 0.34.

The procedure for determining the free energy level of the tetrahedral intermediate in an acyl-transfer reaction can now be specified:

(1) Prepare the ortho acid derivative analogous to the desired intermediate, with OMe or OEt replacing the OH groups of the intermediate.

(2) Determine the heat of hydrolysis of the ortho ester analogue in a suitable acidic solvent. This is heat of reaction calorimetry, and can be carried out by using a simple Dewar calorimeter. The technique is easily learned and requires nothing like the sophistication of equipment and expertise required for combustion calorimetry. From the heat of hydrolysis and the heats of formation of the other reactants and products, one can calculate the heat of formation of the ortho ester analogue.

(3) Calculate the heat of vaporization and the standard entropy of the ortho acid derivative by using accepted estimation procedures. This will lead to the standard free energy of formation of the gaseous analogue.

(4) Either from the solubility and vapor pressure or by direct measurement (which is straightforward, if somewhat tedious),¹⁴ determine the free energy of transfer from the gas phase to aqueous solution, and hence the free energy of formation of the analogue in aqueous solution.

(15) Johnson, S. L. *Adv. Phys. Org. Chem.* **1967**, *5*, 237. Kirby, A. J. In "Comprehensive Chemical Kinetics"; Bamford, C. H., Tipper, C. F. H., Eds.; Elsevier: New York, 1969; Vol. 11, p 57.

(16) Benson, S. W. *J. Am. Chem. Soc.* **1958**, *80*, 5151.

(17) Pihlaja, K.; Kankare, J. *Acta Chem. Scand.* **1969**, *23*, 1745. Pihlaja, K. *Acta Chem. Scand.* **1971**, *25*, 451.

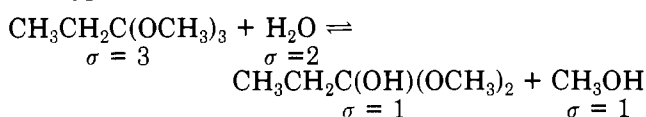
(5) Calculate the free energy change for the hypothetical hydrolysis reaction from the ortho acid derivative to the tetrahedral intermediate from the σ^* values of the substituents and eq 3; include corrections for steric or symmetry effects.

(6) Calculate the free energy of formation of the tetrahedral intermediate from the free energies of formation of the ortho acid analogue, water, and the alcohol released in the hypothetical hydrolysis and the free energy change calculated for this hydrolysis.

(7) From the free energies of formation of the nucleophile and the acyl derivative starting material (which if necessary can be determined by heat of reaction calorimetry as described for the ortho acid derivative) the free energy change for the addition reaction leading to the tetrahedral intermediate can be calculated.

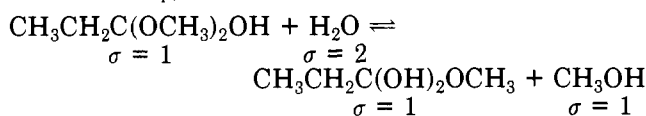
Steps 1-4 are relatively straightforward thermodynamic measurements and calculations; the novelty of our approach is in steps 5 and 6. It may be useful to illustrate the procedure for one example. I will use the intermediate from the addition of water to methyl propionate.¹² The ortho acid analogue is trimethyl orthopropionate; standard thermodynamic procedures lead to values of $\Delta G_f^\circ(\text{aq})[\text{CH}_3\text{CH}_2\text{C}(\text{OCH}_3)_3] = -87.48 \pm 1.19$ and $\Delta G_f^\circ(\text{aq})[\text{CH}_3\text{CH}_2\text{COOCH}_3] = -78.443 \pm 1.19$.

We can now calculate the free energy change for the two hypothetical hydrolysis reactions. We use the sum



$$\sum \sigma^* = 3.52 \quad \Delta G'' = -1.03$$

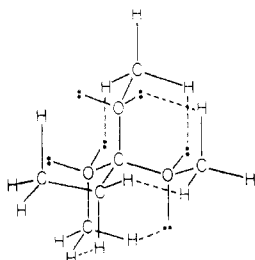
$$RT \ln (\sigma_p/\sigma_r) = -1.36 \quad \text{steric corr} = -0.92$$



$$\sum \sigma^* = 3.05 \quad \Delta G'' = -0.80$$

$$RT \ln (\sigma_p/\sigma_r) = -0.41 \quad \text{steric corr} = -0.92$$

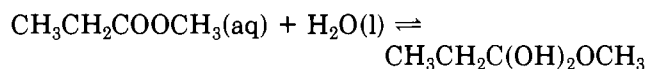
of the σ^* values for the three substituents on the reacting C-OCH₃ and calculate $\Delta G''$ from eq 3. We use only the external symmetry numbers, σ , for the symmetry correction because the internal symmetry contributions, from rotation of methyl groups, will cancel for the processes of interest. In order to determine the steric correction we draw the molecule on a diamond lattice



and count the number of interactions. For each of the first two hydrolysis steps, one H-H and one H-lone pair interaction is relieved. Following Pihlaja¹⁷ we take these as 0.77 and 0.15 kcal/mol, respectively. For the two hydrolyses combined the total free energy change is

-5.44 kcal/mol; this leads to a value for $\Delta G_f^\circ(\text{aq})[\text{CH}_3\text{CH}_2\text{C}(\text{OH})_2\text{OCH}_3] = -122.24 \pm 1.29$ kcal/mol.

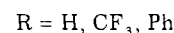
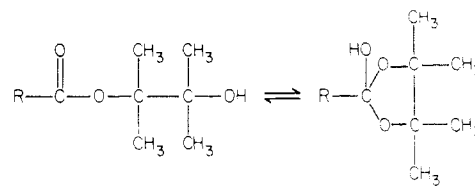
Finally we are able to calculate the free energy change for the process of interest:



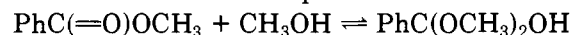
$$\Delta G = 12.86 \pm 1.67 \text{ kcal/mol}$$

Tests of the Method. We have endeavored to test our method to ensure that the answers given by it are valid. This seemed imperative, since the quantities that we are estimating are almost invariably not susceptible to direct measurement. One test is that the equilibrium constants for addition of methanol to esters, RCOOMe,⁵ or of water to a larger set of such esters¹⁴ gave linear free energy plots with σ^* for the acyl substituent, R, with ρ^* similar to, although distinctly larger than, the ρ^* for addition to the analogous series of ketones (and acetaldehyde), RCOMe.¹⁸ This proves that our method leads at least to internally consistent numbers.

It has also proven possible to compare our values for equilibrium constants with values reported for some cases where experimental evaluation has been possible. An indirect comparison is possible for the cyclization reactions of pinacol mono(trifluoroacetate), for which



direct determination of the equilibrium constant for cyclization to the hemi(ortho ester) has been reported,¹⁹ and for pinacol monobenzoate, for which indirect determination of the equilibrium constant for cyclization can be achieved by measuring the forward and reverse rate constants.²⁰ It was possible to determine the free energy of formation of 2-ethoxy-4,4,5,5-tetramethyl-1,3-dioxolane, the ortho ester analogue of the cyclization product from pinacol monoformate, and by our thermochemical method derive the equilibrium constant for cyclization of pinacol monoformate.⁸ Since the effect on ester addition reactions of going from formate to benzoate or trifluoroacetate is known from our studies of esters,^{5,14} it was possible to calculate equilibrium constants for the cyclization of the other pinacol monoesters. The agreement was satisfactory.^{8,20} A more direct test is possible from work by McClelland,²¹ which led to a kinetic determination of the equilibrium constant for addition of methanol to methyl benzoate, $K = 2.2 \times 10^{-12} \text{ M}^{-1}$.²¹ This equilibrium constant can be



directly compared with the value derived from the heat of formation of trimethyl orthobenzoate, $K = 1.5 \times 10^{-12} \text{ M}^{-1}$.^{14,21} The agreement is excellent, and constitutes a strict test of our method.

(18) Greenzaid, P.; Luz, Z.; Samuel, D. *J. Am. Chem. Soc.* **1967**, *89*, 749.

(19) Hine, J.; Ricard, D.; Perz, R. *J. Org. Chem.* **1973**, *38*, 110.

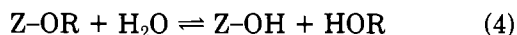
(20) McClelland, R. A.; Ahmad, M.; Bohonek, J.; Gedge, S. *Can. J. Chem.* **1979**, *57*, 1531.

(21) McClelland, R. A.; Patel, G. *J. Am. Chem. Soc.* **1981**, *103*, 6912.

Generalization of the Method. The method just described for estimating the free energy change for replacement of an OR group bound to a tetrahedral carbon by an OH group has proven very useful (vide infra), but there are numerous cases where it would be helpful to apply a similar approach to species where the OR is bound to something other than a tetrahedral carbon, whether this be a trigonal carbon or another element. Accordingly we have sought alternative ways of expressing the dependence of the equilibrium constant for analogues of eq 2 upon the electronic properties of the atom to which OR or OH is attached.

The property measured by σ^* is electron withdrawal (or release) by the substituents; another property of molecules that has long been recognized as strongly dependent upon electron withdrawal or release is the acidity of the corresponding species with OH on the central atom. In fact this should be a very good measure of the electronic effects upon the OH or OR group, provided that the major factor governing the acidity of the species with an OH group is an inductive or field effect, but not if resonance is important in governing the acidity. The reason for this is that resonance will normally alter the acidity of an oxygen acid by delocalization of the charge in the conjugate base, and this type of effect is qualitatively different from other polar effects and completely missing in those acids where only polar interactions govern the acidity.

To test the validity of this approach, the available data for reaction 4 for cases where the pK_a of the cor-



responding OH compound was known were plotted as shown in Figure 2.¹⁰ The line⁶ corresponds to

$$\Delta G'' = -4.78 \pm 0.28 + (0.336 \pm 0.024) pK_a \quad (5)$$

The answer seems to be quite clear that for all compounds where the acidity of the OH group is not affected by $p\pi-p\pi$ resonance phenomena there is a good linear correlation. The correlation extends over a range of 20 powers of 10 in acidity. Compounds where the acidity of the OH group is largely determined by $p\pi-p\pi$ resonance (nitric, nitrous, formic, acetic, and carbonic acids) are markedly divergent from the correlation line. This correlation was used for a discussion of phosphorus compounds and intermediates in phosphoryl transfer.⁶ For some inorganic anions such as phosphate, sulfate (and their derivatives), and perchlorate it is possible to write resonance contributing forms; however these forms necessarily involve $d\pi-p\pi$ bonding, and in recent years the once strong belief in the importance of such bonding has waned considerably.²² Simple electrostatic calculations can be used to predict the pK_a values of many inorganic acids,²³ both those for which π bonding of the sort which might be postulated for phosphate can be written and those (such as telluric acid) for which it cannot. In any case there appear to be no systematic deviations attributable to $d\pi-p\pi$ resonance effects.

Although it should be possible to improve the correlation lines as more and better data become available, it seems that we now have enough information to apply our method to a wide range of problems in both organic and inorganic chemistry.

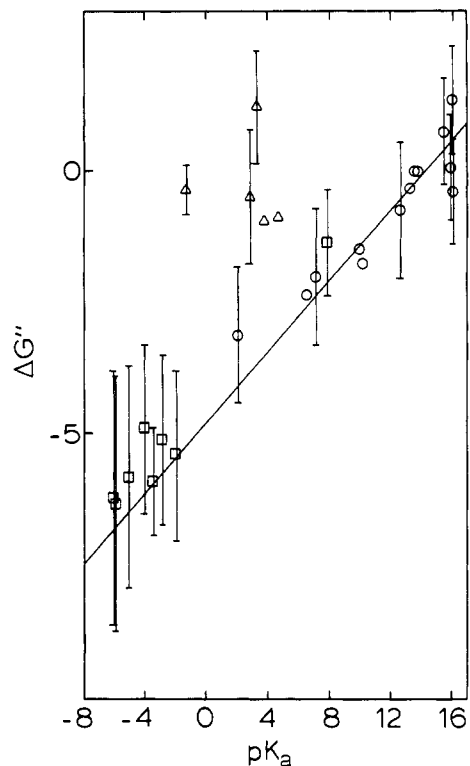


Figure 2. Graph of $\Delta G''$ vs. pK_a for the X-OH compound formed upon hydrolysis: the reaction is $X-OR + H_2O = X-OH + ROH$. The line is calculated by using the slope and intercept reported in ref 6. (O) Points for compounds reported in ref 6; (□) points for inorganic acids without resonance (from ref 10); (Δ) points for acids in which resonance is important (from ref 10). Points without error bars are based on directly measured equilibrium constants: hydrolyses of esters, ratios of equilibrium constants for hemiacetal and hydrate formation from aldehydes or ketones. Points with error bars are calculated from thermodynamic data.

Applications

Acyl Transfer Reactions. The initial applications of our method were to acyl transfer reactions.^{2,3,5,7,8,14} The preparation of suitable ortho acid derivatives (ortho esters,^{2,5,8} amide acetals,³ or monothio ortho esters⁷) allowed the determination of their free energies of formation, which made the determination of the equilibrium constants for the corresponding addition reactions leading to the analogous tetrahedral intermediates in acyl-transfer reactions possible. As an example of the sort of detailed reaction coordinate diagram which can now be drawn we present Figure 3,⁷ which shows the kinetically significant paths at three pH values for a thio ester. The free energy levels for the intermediates are based upon our thermodynamic calculations; the free energies of the transition states are based on the work of Schmir et al.,²⁴ who established the mechanism shown in Scheme I; we have added the zwitterionic intermediate we believe⁷ is involved as an intermediate on the k_1, k_2 path, although it is not required by Schmir's data. With such diagrams it is possible to see more clearly why the various changes in rate-determining step occur as the free energy levels of intermediates and transition states move up or down with changing pH.

Table I has a summary of the equilibrium constants for hydration determined by our thermochemical

(22) Wallmeier, H.; Kutzelnigg, W. *J. Am. Chem. Soc.* **1979**, *101*, 2804.
 (23) Kossiakoff, A.; Harker, D. *J. Am. Chem. Soc.* **1938**, *60*, 2047.

(24) Hershfield, R.; Schmir, G. L. *J. Am. Chem. Soc.* **1972**, *94*, 1263; **1972**, *94*, 6788; **1973**, *95*, 3994.

Table I
Equilibrium Constants for Hydration of Carbonyl Compounds^a

compd	log <i>K</i>	compd	log <i>K</i>	compd	log <i>K</i>
H ₂ CO	3.36 ^b	PhCOCH ₃	-5.18 ^{f,k}	MeOCH ₂ COOMe	-9.21 ^{d,k}
CH ₃ CHO	0.02 ^c	NCCH ₂ COOMe	5.87 ^{h,k}	EtCOOMe	-9.43 ^{d,k}
CF ₃ COOCH ₃	-0.9 ^{d,e}	HCOOMe	-6.6 ^{d,i,k}	PhCOOMe	-10.07 ^{d,k}
PhCHO	-2.08 ^{f,k}	ClCH ₂ COOMe	-6.66 ^{h,k}	iPrCOOMe	-10.42 ^{d,k}
CF ₃ COSEt	-2.8 ^e	PhCOPh	-6.93 ^{f,k}	HCONMe ₂	-13.8 ^{j,k}
CH ₃ COCH ₃	-2.86 ^g	MeCOOMe	-8.2 ^{d,i,k}	MeCONMe ₂	-14.2 ^{j,k}
HCOSEt	-3.5 ^{e,k}				

^a All in aqueous solution at 25 °C. The standard state for all solutes was 1 M solution with an infinitely dilute reference state; the standard state for water was the pure liquid. ^b Reference 26. ^c Kurz, J. L. *J. Am. Chem. Soc.* **1967**, *89*, 3524. ^d Reference 5. ^e Reference 7. ^f Reference 9. ^g Hine, J.; Redding, R. W., *J. Org. Chem.* **1970**, *35*, 2769. ^h Reference 14. ⁱ Reference 2. ^j Reference 3. ^k Calculated by using thermodynamic calculations that are described in the text.

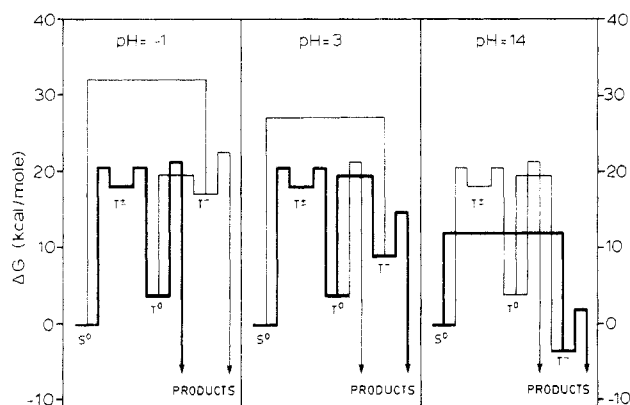
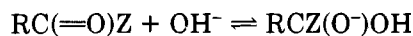


Figure 3. Detailed reaction coordinate diagrams for the hydrolysis of *S*-ethyl trifluorothioacetate at several pH values. S⁰ is the neutral substrate; T[±], T⁰, and T⁻ are the zwitterionic, neutral, and anionic forms of the tetrahedral intermediates. Free energy levels of intermediates were calculated as described in the text. Free energy levels of transition states were calculated from the rate constants for addition or expulsion. Free energies of activation for proton transfer steps were calculated by assuming that these reactions occurred at diffusion-controlled rates in the thermodynamically favored direction. The heavy lines represent the paths of lowest free energy at each pH. As the pH changes the free energy of T⁻, and of transition states with the same composition as T⁻, changes relative to that of T⁰, and the nature of the path of lowest free energy changes.

methods, plus a few additional values for simple carbonyl compounds added as reference values. For all of these esters (including simple alkanooates, aliphatic esters with electronegative substituents, and methyl benzoate) when the logarithm of the rate constant for hydroxide ion attack is plotted vs. the logarithm of the



equilibrium constant for hydroxide ion addition (calculated from the equilibrium constant for water addition using pK_w and an estimated pK_a for the tetrahedral intermediate)^{7,14} a smooth curve fitting all of the data for acyl derivatives within experimental error is obtained (see Figure 4). This curve is based upon Marcus theory;²⁵ although we consider the ability to construct Marcus curves to be one of the major potential advantages of our indirect methods for evaluation of equilibrium constants, space does not permit a proper discussion of this theory or its implications in the present Account. The power of this correlation curve lies in the

(25) Cohen, A. O.; Marcus, R. A. *J. Phys. Chem.* **1968**, *72*, 4249. Marcus, R. A. *J. Am. Chem. Soc.* **1969**, *91*, 7224. Marcus, R. A. *Annu. Rev. Phys. Chem.* **1964**, *15*, 155 and references cited therein. Kresge, A. J. *Rev. Chem. Soc.* **1973**, *2*, 475. Murdoch, J. R. *J. Am. Chem. Soc.* **1972**, *94*, 4410.

Scheme I

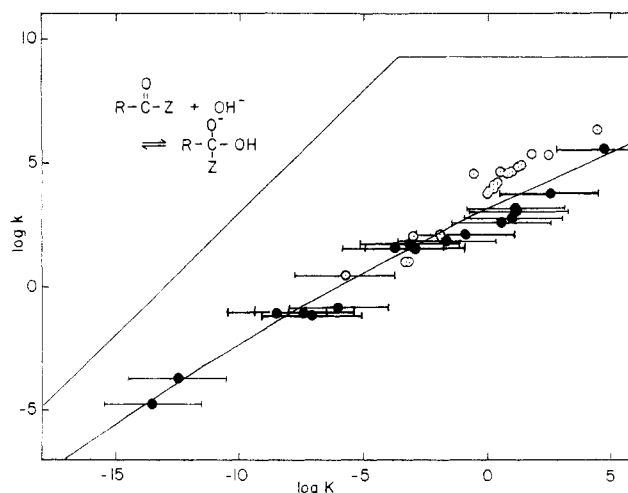
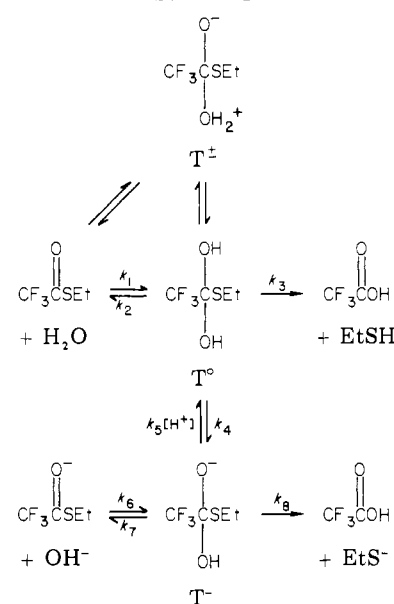


Figure 4. Marcus plot for addition of hydroxide to carbonyl compounds. Points without error bars are for aldehydes and ketones for which the equilibrium constant is directly measured; points with error bars are for acyl derivatives for which equilibrium constants are derived from thermochemical measurements. The compounds included are amides, esters (either methyl esters of various acids, or formate esters of various alcohols and phenols), thio esters, aldehydes, ketones, and formaldehyde. The curve is calculated as described in ref 14.

fact that we now have a means for estimating equilibrium constants for addition to other esters, starting from the rate constants for hydroxide addition, which are available in the literature for many esters, rather

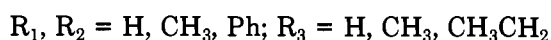
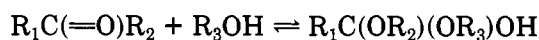
Table II
Free Energies of Addition Reactions
of Phosphoric Acid and Its Esters^a

reaction	log K
$\text{H}_2\text{O} + \text{H}_3\text{PO}_4 = \text{P}(\text{OH})_5$	-12.2 ± 2.2
$\text{H}_2\text{O} + \text{EtOPO}_3\text{H}_2 = \text{EtOP}(\text{OH})_4$	-11.6 ± 2.4
$\text{H}_2\text{O} + (\text{EtO})_2\text{PO}_2\text{H} = (\text{EtO})_2\text{P}(\text{OH})_3$	-11.6 ± 2.0
$\text{H}_2\text{O} + (\text{EtO})_3\text{PO} = (\text{EtO})_3\text{P}(\text{OH})_2$	-10.3 ± 2.7
$\text{HO}^- + (\text{EtO})_3\text{PO} = (\text{EtO})_3\text{P}(\text{OH})\text{O}^-$	-2.8 ± 2.8
$\text{HO}^- + (\text{EtO})_3\text{PO}_2^- = (\text{EtO})_2\text{P}(\text{OH})(\text{O})_2^{2-}$	-16.0 ± 2.4
$\text{HO}^- + (\text{EtO})\text{PO}_3^{2-} = (\text{EtO})\text{P}(\text{OH})(\text{O})_3^{3-}$	-27.3 ± 3.0

^a Adapted from a more extensive table in ref 6.

than starting with the preparation of ortho esters, and performing appropriate measurements. The values so obtained permit satisfactory correlations of rate constants for water- and acid-catalyzed hydrolyses by the Marcus equation.

Carbonyl Compounds. For aldehydes and ketones it is often possible to measure the equilibrium constant for addition reactions involving water or alcohols as

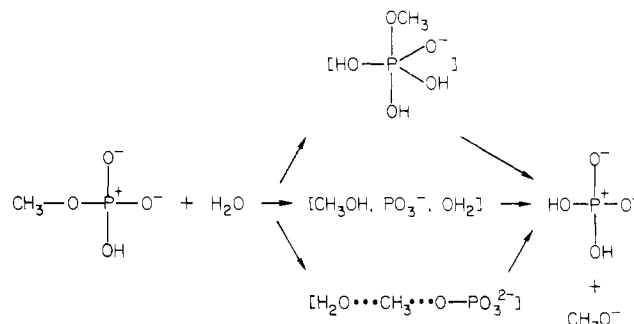


nucleophiles,^{18,26} however as the compounds become less reactive to addition, the measurements become more and more difficult, and to date none has been reported for compounds less reactive than acetone. For alkyl ketones and aralkyl ketones it is possible to measure the equilibrium constant for ketal formation in methanol,²⁷ but for diaryl ketones no such measurements have been reported. For benzophenone, it has been possible to measure the equilibrium constant for transacetalization from triethyl orthoformate.^{28,29} For all of these cases where an equilibrium constant for formation of the acetal is available directly or indirectly, our methods permit the calculation of the equilibrium constants for hemiacetal or hydrate formation.⁹ Equilibrium constants deduced in this way are found in Table I. The set of equilibrium constants for hydration of typical examples of the various classes of simple carbonyl compounds shown in Table I are of considerable pedagogic utility because they give a more solid feel for the reactivity of these classes of compound than can be conveyed by qualitative statements. In particular the descriptive treatment in standard textbooks does not make it clear to students that addition to acetophenone or benzophenone is comparable in difficulty to addition to aliphatic esters.

For simple carbonyl compounds as well it was found that when $\log k$ for hydroxide addition was plotted vs. $\log K$, the points fell close to the curve for esters. Thus, it appears that for all classes of carbonyl derivatives examined to date, the data for hydroxide addition fall, approximately, on a single curve. Not unexpectedly, it seems that each family of compounds defines a

slightly different curve; the phenomenon of a general pattern modified by a dispersion into closely related curves has been encountered rather frequently in physical organic chemistry.³⁰

Phosphate Esters. Compared to carboxylate ester reactions, phosphate ester hydrolyses have proven more difficult and less attractive to study for a number of reasons, despite their considerable chemical, technical, and biological importance.³¹ First of all, the reactions



are inherently slower than the reactions of analogous carboxylate esters with comparable leaving groups. Second, there is a considerable potential for mechanistic confusion, since there are three frequently competitive paths, namely: (i) attack at phosphorus to give a pentavalent intermediate, which may be so short-lived that the reaction approaches or even becomes a direct displacement; (ii) unimolecular cleavage to give a metaphosphate intermediate; and (iii) attack at carbon to give products of nucleophilic substitution. It has been necessary to sort out these possibilities carefully to assign mechanistic significance to rate constants.

For the mechanistic paths involving attack of water or hydroxide at phosphorus, the situation is very similar to that for carboxylate esters. The pentacoordinate intermediate is detectable only in very special circumstances,^{32,33} but there exist stable alkoxy analogues, such as pentaethoxyphosphorane.³⁴ The same procedure as before can now be employed; by hydrolyzing a sample of the phosphorane in a calorimeter, the heat of formation can be determined, and thence the free energy of formation of the pentaethoxyphosphorane.⁶ Then, by using our estimation procedure to calculate the free energy changes for the hypothetical hydrolysis reactions leading to the desired pentacoordinate intermediates, it is possible to calculate the free energy of formation of these intermediates and so the free energies of hydration of phosphate esters (see Table II). This reveals that the slow rates of hydrolysis of phosphate esters, although partly a consequence of the thermodynamic instability of the intermediates in the reactions, are at least as much a consequence of the high kinetic barriers to breakdown of the intermediates.

Phosphites. Our method permits the evaluation of tautomeric equilibrium constants in phosphite chem-

(26) Le Henaff, P. *Bull. Soc. Chim. Fr.* 1968, 4687. Stewart, R.; van Dyke, J. D. *Can. J. Chem.* 1970, 48, 3961. Le Henaff, P. *C. R. Hebd. Seances Acad. Sci.* 1967, 265C, 175. Hooper, D. L. *J. Chem. Soc. B* 1967, 169. Maltz, H. *Chem. Commun.* 1968, 843. Maltz, H., Ph.D. Thesis, Yale University, New Haven, CN, 1967. Le Henaff, P. *C. R. Hebd. Seances Acad. Sci.* 1966, 262C, 1667.

(27) Bell, J. M.; Kubler, D. G.; Sartwell, P.; Zepp, R. G. *J. Org. Chem.* 1965, 30, 4284.

(28) Pfeiffer, G. J.; Adkins, H. *J. Am. Chem. Soc.* 1931, 53, 1043.

(29) We are currently reinvestigating this equilibrium and developing a new method for measuring such equilibrium constants.

(30) For another example of the phenomenon, see: Arnett, E. M.; Mitchell, E. J.; Murty, T. S. S. R. *J. Am. Chem. Soc.* 1974, 96, 3875.

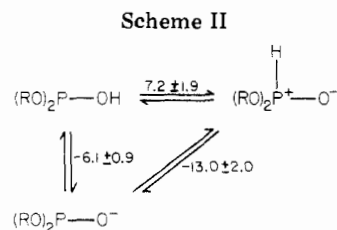
(31) Bruice, T. C.; Benkovic, S. J. "Bioorganic Mechanisms"; Benjamin: New York, 1966; Vol. 2, Chapter 5. Benkovic, S. J.; Schray, K. J. *Enzymes, 3rd Ed.* 1970-1971. 1970, 8, pp 201-238.

(32) Ramirez, F.; Nowakowski, M.; Marecek, J. F. *J. Am. Chem. Soc.* 1977, 99, 4515.

(33) Granoth, I.; Martin, J. C. *J. Am. Chem. Soc.* 1978, 100, 5229.

(34) Denney, D. B.; Relles, H. M. *J. Am. Chem. Soc.* 1964, 86, 3897.

Denney, D. B.; Gough, S. T. D. *Ibid.* 1965, 87, 138. Denney, D. B.; Jones, D. H. *Ibid.* 1969, 91, 5821. Ramirez, F. *Acc. Chem. Res.* 1968, 1, 168.



istry.³⁵ Trialkyl phosphites are known to have three alkoxy groups bonded to phosphorus; dialkyl phosphites by contrast have not tricoordinate but tetracoordinate phosphorus, the expected P-OH having tautomerized to P(H)⁺-O⁻. In dialkyl phosphites the PH bond is known to be ionizable, and many reactions of phosphite diesters are known to involve removal of this hydrogen as the first step. The equilibrium constant for the tautomeric equilibrium is, however, unknown.

The heats of formation of triethyl and diethyl phosphites can be calculated from data in the literature, and so the free energies of formation of these esters in aqueous solution were derived.¹¹ Then, by applying our method to triethyl phosphite, the free energy of formation of the unknown tautomer of diethyl phosphite was readily calculated. Knowing the free energies of the phosphite and the phosphonate tautomers, it was at once possible to calculate the tautomeric equilibrium constant. By estimating the pK_a values for the species it was possible to calculate the tautomeric equilibrium constants for each ionic species, and, finally, to estimate the pK_a value for the P-H bond. Furthermore, similar calculations could be carried out for the monoesters and the free acids, so that a complete description of the system was possible. The set of equilibria involved is shown in Scheme II, which gives log K values.

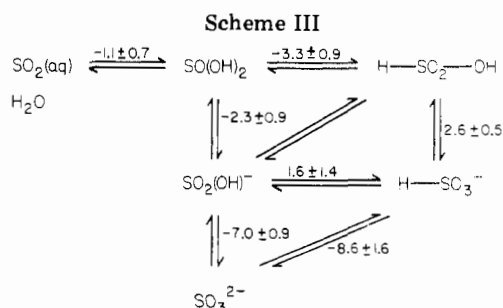
Sulfites. Another inorganic system whose interpretation has long been somewhat confused is that of sulfur dioxide in water,³⁶ although there is good spectroscopic evidence that the major sulfur species in such solutions is SO₂,³⁷ the solubility of SO₂ is surprisingly high, and the acidity of the solutions is that expected if the predominant species were SO(OH)₂.³⁸ In order to investigate this situation further, we calculated the free energy of formation of aqueous dimethyl sulfite from literature heat of formation data, and then calculated the free energy of formation of SO(OH)₂ from this in the usual way.¹³ By comparison with the free energy of formation of the equilibrium mixture corresponding to sulfur dioxide in water, it was possible to show that the major species must indeed be free SO₂. The answer to the problem of anomalous acidity lies in the presence of another species, sulfonic acid, H-SO₂(OH), for which we estimate a pK_a of -2.6. From the pK_a values estimated for the two acids, the tautomeric equilibria can be calculated for various pH's. One interesting result of this analysis is that the major species for "bisulfite" is predicted to be H-SO₃⁻; this is supported by a report that the Raman spectrum of "bisulfite" solutions shows a band for an S-H stretch.³⁹

(35) Kirby, A. J.; Warren, S. G. "The Organic Chemistry of Phosphorus"; Elsevier: London, 1967; p 21.

(36) Schmidt, M.; Siebert, W. In "Comprehensive Inorganic Chemistry"; Trotman-Dickenson, A. F., Ed.; Pergamon: Oxford, 1973; p 878.

(37) Falk, M.; Giguere, P. A. *Can. J. Chem.* 1958, 36, 1121.

(38) Bell, R. P. "The Proton in Chemistry", 2nd ed.; Cornell University Press. Ithaca, NY, 1973; p 92.



That bisulfite is predominantly H-SO₃⁻ is consistent with some qualitative facts of sulfur chemistry: (i) "... there is no example of a reaction in aqueous solution involving bisulfite as a nucleophile";⁴⁰ and (ii) there is a facile free-radical addition of bisulfite to alkenes,⁴¹ which is more readily rationalized in terms of H abstraction from H-SO₃⁻.⁴² Scheme III shows the set of equilibria involved, with log K values.

Enols. The enols of β-dicarbonyl compounds are stable compounds, and sometimes the enol is the major tautomer, so that enol intermediates are quite familiar species.⁴³ Thus, it can easily be forgotten that for simple monocarbonyl compounds, the enol tautomer is present in concentrations near to or below the limits of detection even by the most sensitive instrumental techniques presently available.

Once again we have a situation in which an important intermediate is rendered kinetically labile by the presence of a hydroxyl group, while there exist kinetically inert species with the hydroxyl group replaced by an alkoxy. We are able to apply our method once more by starting with the heats of hydrolysis of the enol ethers and proceeding to the free energies of formation in aqueous solution and so to the free energy of formation of the enol.¹² The calculation requires the use of estimated pK_a values that were obtained by starting from the value for acetophenone enol derived by Loudon by an ingenious kinetic method;⁴⁴ more recently a value has been determined by Wirz, who generated the enol by flash photolysis.⁴⁵ The values for enol content so obtained appear to be consistent with the best experimental values available and involve much simpler experimental techniques. In the course of this investigation we have also derived two other methods for obtaining enol contents, not based on thermochemistry, which have led to similar results.^{46,47}

The results of this investigation are shown in Table III; perhaps the most surprising result was the prediction of a rather high enol content for isobutyraldehyde. Very recently Kresge⁴⁸ measured this enol content by a new technique, which for the first time provides a

(39) Simon, A.; Waldeman, K. Z. *Anorg. Allg. Chem.* 1955, 281, 113, 135. Meyer, B.; Peter, L.; Shaskey-Rosenlund, C. *Spectrochim. Acta* 1979, 35A, 345. Johansson, L.-G.; Lindqvist, O.; Vannenberg, N.-G. *Acta Crystallogr., Sect. B* 1980, B36, 2523.

(40) Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* 1978, 100, 1228.

(41) Kharasch, M. S.; May, E. M.; Mayo, F. R. *J. Org. Chem.* 1938, 3, 175.

(42) King, J. F., personal communication.

(43) Forsen, S.; Nilsson, M. In "The Chemistry of the Carbonyl Group"; Zabicky, J., Ed.; Wiley: New York, 1970; Vol. 2, Chapter 3.

(44) Novak, M.; Loudon, G. M. *J. Org. Chem.* 1977, 42, 2494.

(45) Haspra, P.; Sutter, A.; Wirz, J. *Angew. Chem., Int. Ed. Engl.* 1979, 18, 617.

(46) Guthrie, J. P. *Can. J. Chem.* 1979, 57, 797.

(47) Guthrie, J. P. *Can. J. Chem.* 1979, 57, 1177.

(48) Chiang, Y.; Kresge, A. J.; Walsh, P. J. *Am. Chem. Soc.* 1982, 104, 6122. We thank Professor Kresge for permission to refer to this work prior to its publication.

Table III
 Enol Content of Simple Carbonyl Compounds^a

compound	pK _a ⁻ (enol) ^b	-log K _{enol} ^c	
		thermochem ^d	direct meas- urement
CH ₃ CHO	11.1	5.3 (0.6)	6.4 ^o
CH ₃ CH ₂ CHO	11.4	3.9 (1.0)	
(CH ₃) ₂ CHCHO	11.7	2.8 (1.1)	3.9 ^e
CH ₃ COCH ₃	11.8	7.2 (0.9)	5.8 ^{f,g} 5.6 ^h >6 ⁱ 8.84 ^j 8.46 ^k
CH ₃ CH ₂ COCH ₃	12.1	8.3 (1.0)	
CH ₃ CH ₂ COCH ₂ CH ₃	12.1	7.8 (1.)	8.02 ^j
cyclopentanone	12.1	7.2 (1.2)	4.9 ⁱ 4.5 ^{l,m} 3.0 ^{g,m} 8.00 ^k
cyclohexanone	12.1	5.7 (1.1)	5.4 ⁱ 2.1 ^{g,m} 3.6 ^h 6.64 ^k
PhCOCH ₃	11.0	6.7	4.7 ^{l,m} 3.5 ^{f,g} 8.15 ^k

^a All in water at 25 °C; values in parentheses are estimated standard deviations. ^b Estimated as described in ref 12. ^c K_{enol} = [enol]/[keto]. ^d Reference 12. ^e Reference 48. ^f Gero, A. *J. Org. Chem.* 1954, 19, 1960. ^g Extrapolated to neat liquid. ^h Schwarzenbach, G.; Wittwer, C., *Helv. Chim. Acta* 1947, 30, 689. ⁱ Bell, R. P.; Smith, P. W. J. *Chem. Soc. B* 1966, 241. ^j Toullec, J.; Dubois, J. E. *Tetrahedron* 1973, 29, 2851. Dubois, J. E.; Toullec, J. *Tetrahedron* 1973, 29, 2859. ^k Reference 49. ^l Reference 44. ^m In 40% *tert*-butyl alcohol-water. ⁿ Gero, A. *J. Org. Chem.* 1961, 26, 3156. ^o Reference 53.

reliable absolute method for determining enol contents of simple carbonyl compounds; their value is within the published uncertainty limits of our thermochemically derived value. After the initial form of this Account had been submitted we learned that Capon and Zucco⁵³ had measured the pK_{enol} for acetaldehyde as 6.5; this is similar to our value but deviates from it by somewhat more than our estimated uncertainty.

A clear weakness in our thermochemical approach is the assumption that the pK_a of simple enols is not determined by resonance;⁴⁹ this is clearly less valid than was the case for, say, ortho acids, and will become quite incorrect for more complicated enols. Our method is insensitive to pK_a (the slope of a plot of ΔG'' vs. pK_a is 0.34),⁶ and there is reasonable agreement with other methods; it appears that the assumption does not lead to serious error, and is justifiable as an initial approximation.

Relation to Other Work

Fastrez⁵⁰ has developed an interesting and quite different method for estimating the equilibrium constants for addition reactions for simple acyl derivatives.

(49) Dubois, J. E.; El-Alaoui, M.; Toullec, J. *J. Am. Chem. Soc.* 1981, 103, 5393.

(50) Fastrez, J. *J. Am. Chem. Soc.* 1977, 99, 7004.

This method has the advantage of being applicable to a number of classes of compounds where our method would not be easy to apply. Unfortunately the agreement between the two methods is not good: the average difference in log K is 1.97 (rms value). It is in the nature of the methods that this is probably less than the combined uncertainties. Both methods give useful but imprecise values.

Capon has developed methods for generating hemioorthoesters⁵¹ and enols⁵² in solution under conditions suitable for NMR spectroscopy. We were pleased to see that he was able to use our calculated values to pick conditions for these experiments, and that the observed behavior was consistent with our free energy calculations.⁵¹ We have already mentioned work by Kresge,⁴⁸ Capon,⁵³ and McClelland^{20,21} that has confirmed equilibrium constants calculated by our methods.

Prospects

Although we have succeeded in moving a long way toward the goal of specifying a general procedure for determining the free energy levels of intermediates in acyl-transfer and related reactions, there are a number of areas still requiring clarification. For instance, the apparent general correlation between rate and equilibrium constants for hydroxide addition to carbonyl compounds needs to be examined further. Does this hold for variation in the leaving group in esters, aryl esters, thio esters, aryl thio esters, amides, and anilides? If so, then most of the work done on acyl-derivative hydrolysis will be accessible to our method. Can patterns be discerned for addition of other nucleophiles to the classes of compounds for which hydroxide addition gives such simple correlations? If so, then our methods could be applied to acyl-transfer reactions for which an immense body of data exists. Although our approach seems to work for simple enols, it clearly must break down for more complex enols, such as those for β-dicarbonyl compounds for which resonance plays a major role in determining the pK_a; it remains to be seen at what point this breakdown will occur. If appropriate thermochemical data were available it would be instructive to examine the extent of the breakdown of the method for aryl ethers, particularly with substituents, such as *p*-nitro, for which resonance effects should be large.

I gratefully acknowledge financial support for this work from the National Science and Engineering Research Council of Canada, the Alfred P. Sloan Foundation, and the Academic Development Fund of the University of Western Ontario. I thank my colleagues J. F. King and P. de Mayo for helpful discussions. I thank P. A. Cullimore, Dana Zendrowski, and A. N. Klym for careful technical assistance.

(51) Capon, B.; Ghosh, A. K.; Grieve, D. McL. A. *Acc. Chem. Res.* 1981, 14, 306. Capon, B.; Gall, J. H.; Grieve, D. McL. A. *J. Chem. Soc., Chem. Commun.* 1976, 1034. Capon, B.; Grieve, D. McL. A. *J. Chem. Soc., Perkin Trans. 2* 1980, 300.

(52) Capon, B.; Rycroft, D. S.; Watson, T. W.; Zucco, C. *J. Am. Chem. Soc.* 1981, 103, 1761.

(53) Capon, B.; Zucco, C. *J. Am. Chem. Soc.* 1982, 104, 7567. We thank Professor Capon for permission to refer to this work prior to its publication.