

γ -phosphoryl group remains coordinated by the enzyme-bound Mn^{2+} . The distance to the reaction-center α -phosphorus atom (4.2 Å) is most simply explained by the rapid averaging of $\leq 15\%$ inner-sphere coordination with $\geq 85\%$ second-sphere coordination. The resulting polyphosphate conformation is puckered and somewhat strained. Hence an important role of the divalent cation activator in catalysis is to assist the departure of the leaving pyrophosphate group by γ coordination, and possibly to facilitate nucleophilic attack on the α -phosphorus atom by strain and by hydrogen bonding through a coordinated water ligand.¹⁸

A second difference between the binary and ternary complexes is in the conformational angle χ about the thymine-deoxyribose bond of dTTP. The χ value of $40 \pm 5^\circ$ in the binary complex increases to $90 \pm 5^\circ$ in the ternary complex (Figure 7A). Similarly, a 90° torsion angle is also found for the purine nucleotide substrate Mn-dATP when bound to DNA polymerase (Figure 7B).¹⁸ Interestingly, the latter torsion angle of 90° is that found for the deoxynucleotidyl units in double-helical DNA. Hence the binding of the substrate Mn-dTTP to the enzyme, DNA polymerase, in the absence of template, has changed the substrate conformation to that of a nucleotidyl unit in the product—double-helical DNA.

When the structure of enzyme-bound Mn-dTTP is superimposed by computer onto the double-helical structure of DNA-B (Figure 7C), the resulting location of the α -phosphorus atom and the leaving pyrophosphate group of the bound substrate relative to the attacking 3'-OH group of the preceding nucleotide unit is consistent only with an in-line nucleophilic displacement on the α phosphorus.¹⁸ Hence the biosynthesis of nucleic acids, like their hydrolysis,⁴⁴ appears to proceed by an in-line mechanism.

(44) D. A. Usher, E. S. Erenrich, and F. Eckstein, *Proc. Nat. Acad. Sci. U.S.A.*, **69**, 115 (1972).

The selection by the enzyme of those substrate conformations that fit into the double helix would amplify the Watson-Crick base-pairing scheme and would explain the low error rates of DNA polymerases⁴¹ which are at least two orders of magnitude below those predicted by the thermodynamic⁴⁵ and kinetic effects of base-pairing alone.⁴⁶

Conclusions

Numerous examples have been provided which establish that the average conformation of a flexible substrate, when bound to an enzyme, generally differs from that of the free substrate in solution (Figures 1, 4, and 7).

Second-sphere enzyme-metal-(H₂O)-substrate complexes are used by enzymes to polarize carbonyl groups (six examples, Figures 1 and 2) and to position phosphoryl groups for nucleophilic attack (four examples, Figures 4–7). In the case of pyruvate kinase, an additional metal interacts directly with the ATP (Figure 5).

On two-substrate enzymes, such as dehydrogenases (Figure 1), kinases (Figure 5), and even on a biotin enzyme, (Figure 3), close proximity of the two bound substrates is observed, in some cases approaching molecular contact.

The inner coordination sphere of a metal is used to facilitate the departure of the leaving group in DNA polymerase (Figure 7).

*This work was supported by National Institutes of Health Grant AM-13351, by National Science Foundation Grant PCM74-03739, by Grants CA-06927 and RR-05539 to this Institute from the National Institutes of Health, and by an appropriation from the Commonwealth of Pennsylvania. Portions of Figures 1, 4, 5, 6, and 7 have been published in *Journal of Biological Chemistry*, and are reprinted with permission.*

(45) A. S. Mildvan, *Annu. Rev. Biochem.*, **43**, 357 (1974).

(46) E. C. Travaglini, A. S. Mildvan, and L. A. Loeb, *J. Biol. Chem.*, **250**, 8647 (1975).

Structural Effects on the Acid-Catalyzed Hydration of Alkenes

Vincent J. Nowlan and Thomas T. Tidwell*

Department of Chemistry, University of Toronto, Scarborough College, West Hill, Ontario, Canada

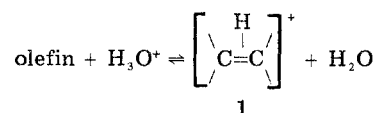
Received February 1, 1977

Acid-catalyzed hydration of olefins, a relatively late entry in the field of mechanistic investigations, was first studied in the early 1930's. At the same time, the anti-Markownikoff addition of HBr to alkenes, which was soon formulated as a free-radical chain process, was

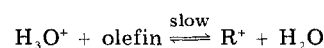
Thomas T. Tidwell is Professor of Chemistry at University of Toronto. He was born in Atlanta, Ga., in 1939, and studied at Georgia Institute of Technology for his B.S. degree. After graduate work at Harvard University, where he received his Ph.D. working with P. D. Bartlett, he went on to postdoctoral research at the University of California, San Diego, and the University of East Anglia. His research is concentrated in mechanistic studies of carbonium ions, carbanions, and free radicals, and the effects of steric crowding.

Vincent J. Nowlan was a Lecturer at University of Toronto, where he received his Ph.D. degree working with G. H. Schmid. He is now carrying out research on tar sands with Syncrude Corp. in Alberta, Canada.

Scheme I



Scheme II



being elucidated.¹ In 1934 Lucas and his co-workers published² measurements of the rate constants for

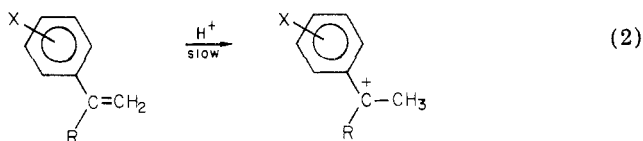
hydration of isobutylene and trimethylethylene, and Whitmore clearly stated³ that the former compound underwent protonation to the *tert*-butyl cation (eq 1).



In the following decade salt effects on isobutylene hydration were studied by Hammett⁴ and by Kilpatrick,⁵ and in the decade of the '50s the scope of the study was greatly expanded by Taft and his co-workers,⁶ who utilized an array of sophisticated mechanistic criteria (kinetic isotope effects, acidity function dependence, activation parameters, isotopic labeling, and substituent effects).

Taft eventually concluded^{6b} that his evidence for alkene-olefin interconversion was "consistent with either of the mechanisms" whose rate-determining steps for hydration are shown in Schemes I and II. The π complex mechanism (Scheme I) was favored^{6b} and is a variation of his earlier proposal which omitted the water molecule in the rate-determining step. This early proposal was based on the Zucker-Hammett hypothesis, which stipulated that a reaction such as alkene hydration, which followed the acidity function H_0 rather than pH, did not involve water in the rate-determining transition state. Taft later^{6b} felt this criterion was not valid and favored rate-determining rearrangement of the π complex to the "encumbered" carbonium ion (Scheme I).

The next wave of research concentrated on the hydration of substituted styrenes.⁷ The rates of hydration of these compounds were correlated by the Brown-Hammett equation using the electrophilic substituent parameters σ^+ and were subject to general acid catalysis in highly reactive systems.^{7c} The results convincingly established the mechanism as rate-determining protonation on carbon (the A_{SE2} mechanism, eq 2).



A parallel line of development involved study of enol ethers and esters. Enol carboxylates were first studied by Skrabal,^{8a} but it was only after many years and

(1) (a) M. S. Kharasch and F. R. Mayo, *J. Am. Chem. Soc.*, **55**, 2468 (1933); (b) F. R. Mayo and C. Walling, *Chem. Rev.*, **27**, 351 (1940); (c) D. H. Hey and W. A. Waters, *ibid.*, **21**, 169 (1937); for recent work on free-radical addition to olefins see J. M. Tedder and J. C. Walton, *Acc. Chem. Res.*, **9**, 183 (1976).

(2) (a) H. J. Lucas and W. F. Eberz, *J. Am. Chem. Soc.*, **56**, 460 (1934); (b) H. J. Lucas and Y.-P. Liu, *ibid.*, **56**, 2138 (1934).

(3) F. C. Whitmore, *Ind. Eng. Chem.*, **26**, 94 (1934).

(4) G. R. Lucas and L. P. Hammett, *J. Am. Chem. Soc.*, **64**, 1938 (1942).

(5) F. G. Ciapetta and M. Kilpatrick, *J. Am. Chem. Soc.*, **70**, 639 (1948).

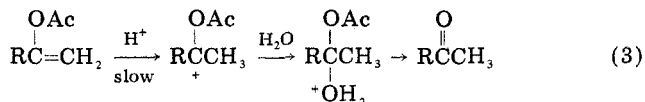
(6) (a) J. B. Levy, R. W. Taft, Jr., D. Aaron, and L. P. Hammett, *J. Am. Chem. Soc.*, **73**, 3792 (1951); (b) R. H. Boyd, R. W. Taft, Jr., A. P. Wolf, and D. R. Christman, *ibid.*, **82**, 4729 (1960); and intervening papers. Although all of Taft's results have not been published in primary journals they have been widely quoted in secondary references: P. D. Bartlett and G. D. Sargent, *ibid.*, **87**, 1297 (1965); P. B. D. de la Mare and R. Bolton, "Electrophilic Additions to Unsaturated Systems" Elsevier, Amsterdam, 1966.

(7) (a) N. C. Deno, F. A. Kish, and H. J. Peterson, *J. Am. Chem. Soc.*, **87**, 2157 (1965); (b) W. M. Schubert and B. Lamm, *ibid.*, **88**, 120 (1966); (c) W. M. Schubert, B. Lamm, and J. R. Keefe, *ibid.*, **86**, 4727 (1964); (d) W. M. Schubert and J. R. Keefe, *ibid.*, **94**, 559 (1972); (e) J.-P. Durand, M. Davidson, M. Hellin, and F. Coussemant, *Bull. Soc. Chim. Fr.*, **43**, 52 (1966).

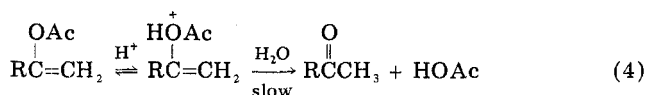
Table I
Rates of Hydration of Vinyl Phosphates and Solvolysis of *p*-Nitrobenzoates

R	$k_{rel}(\text{RC}(\text{OPO}_3\text{Et}_2)=\text{CH}_2)$	$k_{rel}(\text{RCMe}_2\text{-OPNB})^{12}$
Me	1.0	1.0
Ph	0.64	969
c-Pr	0.60	700×10^3

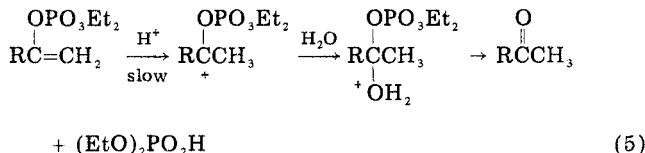
several incorrect reports that their mechanism of reaction became clear: when these compounds had another electron-donating α substituent on the double bond, they also were favored to react by the A_{SE2} mechanism of rate-determining protonation on carbon (eq 3).⁸ If the double bond was not activated, these



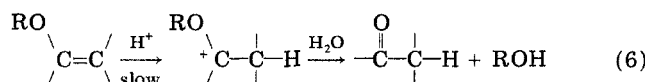
compounds reacted by the normal A_{AC2} mechanism of ester hydrolysis (eq 4).⁸ Enol phosphates were found



to react exclusively by the A_{SE2} route (eq 5),⁹ as the



conceivable A_{AC2} hydrolysis was too slow to compete. The earlier reports had favored a variant, with P-O bond breaking, which was excluded by isotopic-labeling studies.^{9a,d} The reactivity of enol ethers was also examined by Skrabal at an early date,^{10a} and the high reactivity of these compounds, as well as the observed general acid catalysis,^{10b-d} led to the quick acceptance of the A_{SE2} mechanism for their reactions (eq 6).



Finally, in 1971 it was found that 2,3-dimethyl-2-butene and *trans*-cyclooctene underwent hydration with general acid catalysis, confirming the A_{SE2} mechanism for these compounds and, by analogy, for other alkenes as well.¹¹

In addition to revealing the mechanism of alkene hydration, these studies were an important proving ground for testing many of the basic tools for the study

(8) (a) A. Skrabal and A. Zahorka, *Monatsh Chem.*, **48**, 459 (1927); (b) A. F. Rekasheva, *Usp. Khim.*, **37**, 1009 (1968); (c) D. S. Noyce and R. M. Pollack, *J. Am. Chem. Soc.*, **91**, 119, 7158 (1969); (d) E. K. Euranto and L. Hautoniemi, *Acta Chem. Scand.*, **23**, 1288 (1969); (e) K. Yates, *Acc. Chem. Res.*, **4**, 136 (1971).

(9) (a) E. P. Lyznicki, Jr., and T. T. Tidwell, *J. Am. Chem. Soc.* **95**, 4935 (1973); (b) R. D. Frampton, T. T. Tidwell, and V. A. Young, *ibid.*, **94**, 1271 (1972); (c) C. A. Bunton and L. Robinson, *ibid.*, **91**, 6072 (1969); (d) C. Triantaphylides, G. Peiffer, and R. Gerster, *Bull. Soc. Chim. Fr.*, 1756 (1973); (e) A. Arcoria, S. Fisichella, and F. Sardo, *J. Org. Chem.*, **37**, 2612 (1972); (f) F. W. Lichtenthaler and F. Cramer, *Chem. Ber.*, **95**, 1971 (1962).

(10) (a) A. Skrabal, *Chem. Ber.*, **72**, 446 (1939); (b) D. M. Jones and N. F. Wood, *J. Chem. Soc.*, 5400 (1964); (c) A. J. Kresge, H. L. Chen, Y. Chiang, E. Murrill, M. A. Payne, and D. S. Sagatys, *J. Am. Chem. Soc.*, **93**, 413 (1971); (d) T. Fueno, I. Matsumura, T. Okuyama, and J. Furukawa, *Bull. Chem. Soc. Jpn.*, **41**, 818 (1968).

(11) A. J. Kresge, Y. Chiang, P. H. Fitzgerald, R. S. McDonald, and G. H. Schmid, *J. Am. Chem. Soc.*, **93**, 4907 (1971).

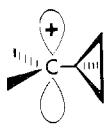


Figure 1.

of organic reaction mechanisms. These included theories of acidity functions, solvent isotope effects, secondary isotope effects, Brønsted relations, the Brown-Hammett equation, and general acid catalysis. However, one area that was relatively neglected was the correlation of the reactivity of the entire group of alkenes with structure. Noyce^{8c} compiled the available rate ratios for the various classes of alkenes and compared the effects of methyl and phenyl substitution on their reactivity. The effects were compared to the corresponding effects on solvolysis reactions, and ground-state stabilization effects were also considered, but a quantitative account of the effects of the substituents did not emerge.

Our interest in the general problem of structural effects on alkene hydrations arose from an interest in vinyl phosphate hydrolysis.^{9a,b} The rates of α -arylvinyloxy phosphates could be nicely correlated by the σ^+ parameters of the substituents on the α -aryl group, as expected for the mechanism in eq 5. However, an anomaly arose when the studies were extended to other α substituents. Specifically, the substituent effects in the phosphate hydrolyses (eq 5) were markedly different from the influence of these substituents in ester solvolysis (eq 7),¹² as shown in Table I. At the time



these rates were measured no rates had been reported which showed the effect of the cyclopropyl group on protonation of a double bond. Our measurements showed a large rate acceleration by cyclopropyl; the relative rates for the series $c\text{-PrCH}=\text{CH}_2:n\text{-BuCH}=\text{CH}_2:\text{PhCH}=\text{CH}_2$ were found to be $10^3:1:0.1$.¹³ The large acceleration by the cyclopropyl substituent was in accord with the powerful electron-donating ability of this group when it can attain the bisected conformation adjacent to the carbonium ion center (Figure 1).¹⁴ The failure of the α -cyclopropylvinyl phosphate to show the same acceleration was attributed by one of us¹³ to a strong stabilizing effect of the phosphoryloxy group leveling the donating ability of the cyclopropyl.

In order to provide a better understanding of the effect of substituents on alkene hydrations, it was apparent that a wider range of compounds had to be compared. We set out to assemble a group of representative olefins by our own experimental work and by compiling data available in the literature and also attempted to quantitatively rationalize the effects of structure on reactivity by simple theories based on commonly recognized principles. In our view a theory relying on too many arbitrary parameters or theoretical concepts removed from tangible physical reality would

(12) H. C. Brown and E. N. Peters, *J. Am. Chem. Soc.*, **95**, 2400 (1973).
 (13) D. G. Garratt, A. Modro, K. Oyama, G. H. Schmid, T. T. Tidwell, and K. Yates, *J. Am. Chem. Soc.*, **96**, 5295 (1974).

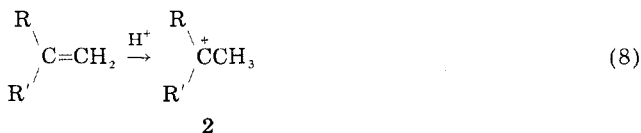
(14) (a) H. C. Brown and J. D. Cleveland, *J. Org. Chem.*, **41**, 1792 (1976), and references therein. (b) It has been argued that the unsubstituted cyclopropylmethylcarbonium ion has a bridged structure under stable ion conditions,^{14c} but this conclusion has been challenged.^{14d} (c) G. A. Olah, *Angew. Chem., Int. Ed. Engl.*, **12**, 173 (1973). (d) W. J. Hehre and P. C. Hiberty, *J. Am. Chem. Soc.*, **96**, 302 (1974).

not be useful for understanding the reactivities.

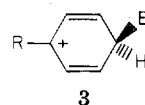
The standard conditions for comparison were chosen as k_2 values ($k_{\text{obsd}}/[\text{H}^+]$) in dilute aqueous acid at 25 °C. This medium imposed limits because of the low solubility of most organic compounds in this solvent. Fortunately, kinetics may be followed at very low olefin concentrations, typically 10^{-3} M or less, by observing the disappearance of the ultraviolet absorption of the olefin during hydration. Commonly available spectrophotometers may be utilized for wavelengths as low as 200 nm, or 185 nm if the oxygen is swept from the instrument by N_2 . Even ethylene, which has a λ_{max} around 175 nm, may be measured by observing the decrease of the residual absorption at 187 nm.

A more fundamental problem was obtaining rates in dilute acid. Many compounds of interest are too unreactive to measure except in quite strong acids. The acidity of these media exceeds the stoichiometric proton concentration, so k_2 values cannot be reliably obtained from $k_{\text{obsd}}/[\text{H}^+]$. It has been found that all examples reacting by rate-determining protonation on carbon give linear correlations of $\log k_{\text{obsd}}$ with acidity functions H_0 or H_R . At low acidities one function or the other is usually preferable, but at higher acidities the functions have been found to be linearly related, so both are satisfactory.¹⁵ We have chosen $H_0 = 0$ as a reference point for extrapolation from higher acidity that is sufficiently close to the dilute acid region. In the cases tested, the rates determined by extrapolation to $H_R = 0$ are almost the same. The slopes of the $\log k_{\text{obsd}}$ vs. H_0 plots are usually near -1.1 , but the extremes range from -0.87 for $(\text{EtO})_2\text{PO}_2\text{CH}=\text{CH}_2$ to -1.54 for $\text{CH}_2=\text{CH}_2$. As discussed below, the long extrapolations of the rates of these unreactive compounds to $H_0 = 0$ give rise to artificially low rates for those compounds with steep acidity dependence.

It was soon apparent that, compared to solvolytic reactions and other additions, there was a relative paucity of data on hydrations of alkenes.¹⁶ Nevertheless, we collected an initial group of 23 1,1-disubstituted alkenes which reacted by the $A_{SE}2$ route (eq 8). These compounds had a spread of second-order



rate constants of 10^{18} at 25 °C in dilute acid which were extrapolated from conditions ranging from water at pH 7 to 1 M HNO_3 at 180 °C. It appeared to us that the interaction of the substituents with the positive charge in intermediate **2** was analogous to that in the electrophilic aromatic substitution intermediate **3**, which



has been found to be correlated by the Brown σ_p^+ parameters. These constants were devised to measure the electronic effect of a group when the substituent has

(15) A. J. Kresge, H. J. Chen, and Y. Chiang, *J. Chem. Soc., Chem. Commun.*, 969 (1972).

(16) (a) G. H. Schmid and D. G. Garratt in "Chemistry of the Alkenes", Vol. 3, J. Zabicky, Ed., Wiley-Interscience, New York, N.Y., 1977; (b) R. Bolton, *Compr. Chem. Kinet.*, **9**, 1 (1973).

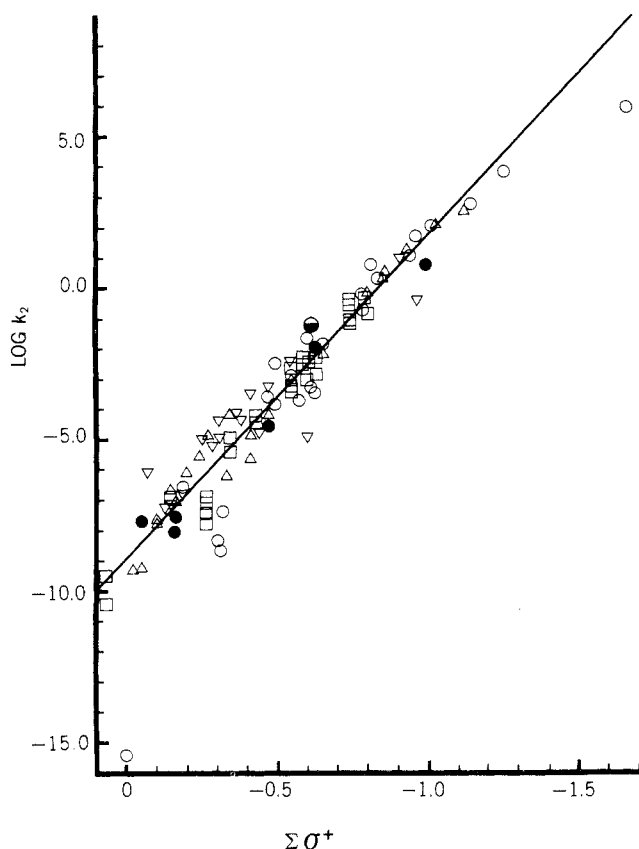


Figure 2. Reactivity in acid-catalyzed alkene protonations. (○) Original set of 1,1-disubstituted alkenes; (●) 1,3-butadienes and 2-bromopropene; (◐) *N*-vinylacetamide; (Δ) substituted styrenes; (▽) vinyl esters; (◻) 1,2-disubstituted alkenes. For the later group the ordinate is the quantity in brackets in eq 14.

a direct resonance interaction with a positive charge.¹⁷ We found that indeed a very satisfactory correlation of the hydration rates could be obtained by eq 9, with a

$$\log k_2 = \rho \Sigma \sigma_p^+ + C \quad (9)$$

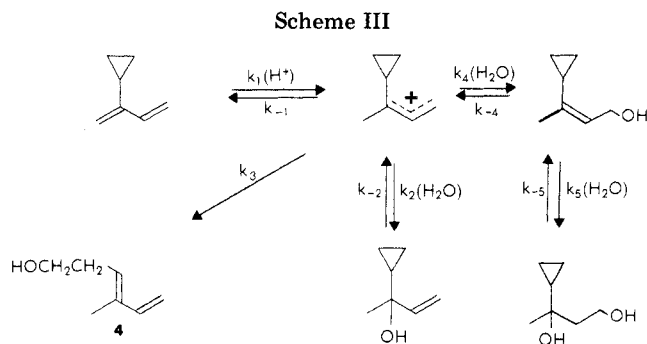
correlation coefficient of 0.970.¹⁸ The most recent data for the original 23 alkenes are shown in Figure 2, together with data for other alkenes measured subsequently.

It would appear that the effect of steric interactions and solvation might be similar in 2 and 3, and that ground-state effects in the precursors to the two series might be related, and the general success of the correlation in Figure 2 appears to vindicate this reasoning. By contrast, a plot of $\log k_2$ vs. the σ_p constants, which do not allow for direct resonance interaction, shows almost random scatter.¹⁸

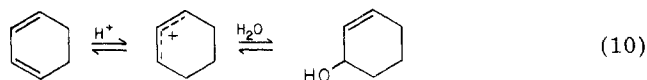
With the success of this initial correlation, it appeared of immediate interest both to test its reliability and generality and to attempt to extend it to new areas. These tests have been pursued with new classes of alkenes, both by measuring new rates and by determining substituent constants where these were unknown. Deviations have been critically examined to determine if the theory appears to be inadequate or whether more accurate experimental results may improve the correlation. Finally, we are using the correlation as a standard by which to judge the effect of structure on other reactions.

(17) H. C. Brown and Y. Okamoto, *J. Am. Chem. Soc.*, **80**, 4979 (1958).

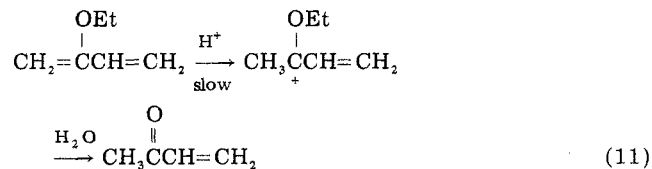
(18) K. Oyama and T. T. Tidwell, *J. Am. Chem. Soc.*, **98**, 947 (1976).



1,3-Butadienes comprise a class of compounds of great utility, but, surprisingly, there has been a dearth of information regarding the kinetics of their reactions. The kinetics of hydration of several cycloalka-1,3-dienes have been studied,¹⁹ and it was found that 1,3-cyclohexadiene reacted by the $A_{SE}2$ path about 30 times faster than styrene (eq 10). Rates have also been



reported for a group of 1- and 2-ethoxy-1,3-butadienes, whose hydration proceeds to give carbonyl derivatives (eq 11).²⁰



The regioselectivity of additions to 1,3-butadienes has been found to vary from >97% 1,2 addition of HCl to isoprene,^{21a} to approximately equal amounts of 1,2 and 1,4 addition in the addition of HCl^{21b} or Br₂^{21c} to 1,3-butadiene itself, and to almost exclusive 1,4 addition to 2-chloro-1,3-butadiene.^{21d,e} A qualitative picture emerges to show that 1,4 addition is favored by diminishing stabilization of a carbonium ion center by the substituent at C-2. A molecular orbital treatment consistent with these results has been presented.^{21f}

We have found it possible to measure rates of hydration of 2-substituted 1,3-butadienes having 2-substituents of H, Me, Cl, and *c*-Pr.²² In addition, the rate of the 2-ethoxy compound in water has been approximated from the reported rate in 80% acetone. As may be seen in Figure 2, these rates fit in the same correlation with the previous set of alkenes. It is of interest that the first measurements we made on the 2-cyclopropyl compound were done in rather strong acid and a slow rate of disappearance of a diene chromophore was observed, leading to a rate constant which deviated substantially from the correlation. Further study revealed, however, that an initial hydration and

(19) (a) J. L. Jensen and V. Uaprasert, *J. Org. Chem.*, **41**, 649 (1976); (b) J. L. Jensen, V. Uaprasert, and R. C. Fujii, *ibid.*, **41**, 1675 (1976); (c) J. L. Jensen, and D. J. Carré, *ibid.*, **36**, 3180 (1971).

(20) (a) J.-P. Gousenard and M. Blain, *Bull. Soc. Chim. Fr.*, 388 (1974); (b) T. Okuyama, T. Sakagami, and T. Fueno, *Tetrahedron*, **29**, 1503 (1973).

(21) (a) Y. Pocker, K. D. Stevens, and J. J. Champoux, *J. Am. Chem. Soc.*, **91**, 4199 (1969); (b) A. L. Henne, H. Chanan, and A. Turk, *ibid.*, **63**, 3474 (1941); (c) L. F. Hatch, P. D. Gardner, and R. E. Gilbert, *ibid.*, **81**, 5943 (1959); (d) L. F. Hatch and S. G. Ballin, *ibid.*, **71**, 1039 (1949); (e) A. A. Petrov, *Zh. Obshch. Khim.*, **13**, 102, 108 (1943); (f) M. D. Jordan, Jr., and F. L. Pilar, *Theor. Chim. Acta*, **10**, 325 (1968).

(22) W. K. Chwang, P. Knittel, K. M. Koshy, and T. T. Tidwell, *J. Am. Chem. Soc.*, **99**, 3395 (1977).

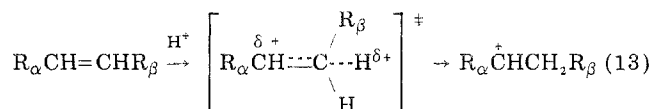
rearrangement had occurred (Scheme III), and that the slow rate being observed was that of the rearranged diene 4.²² The true rate of the unrearranged diene was close to that expected from the correlation, and the slow rate of the rearranged diene was as expected for its structure.

Substituted styrenes had been studied a great deal with respect to varying substitution on the aryl ring. In order to correlate these data, we have equated the substituent effect of the aryl group to that of the unsubstituted phenyl group plus that for the substituent attenuated by a transmission factor τ for the insulation by the aromatic ring (eq 12). The value of the

$$\sigma_p^+(\text{Ph-X}) = \sigma_p^+(\text{Ph}) + \tau\sigma^+(\text{X}) \quad (12)$$

transmission coefficient is found to be 0.2 from the value of the slopes of the rates of two different series of biphenyl vs. phenyl electrophilic reactions.²² The rates available from this procedure are indicated on the plotted correlation of rates (Figure 2) and fit very well.

1,2-Disubstituted alkenes are much more complicated systems than alkenes substituted only on one carbon. In protonations of the former compounds (eq 13) a number of new interactions will be present that



are either invariant or are much less significant in the compounds with a terminal methylene group. Possible interactions include solvation effects, vicinal substituent-substituent interactions in both the ground state and transition states, ground-state stabilization, electronic effects of the β substituent in the transition state, and interactions of the β substituent with the electrophile. We have compiled a set of rates of protonation of 27 1,2-disubstituted alkenes.^{23a} These include all compounds which we have measured or have been able to locate in the literature which react in water at 25 °C according to eq 13 and for which relevant substituent parameters are available, plus a group of compounds, measured by Fueno and co-workers in 80% dioxane,^{23b} whose rates we have converted to rates in water.^{23a}

Two effects of the β substituents on the reactivity of the 1,2-disubstituted alkenes are most important. These are the electronic effect of the groups in the transition state, which can be expressed by the parameter σ_m^+ , and the ground-state stabilization by the group, which can be expressed by the D parameters of Hine and Flachskam.²⁴ The satisfactory fit of the data by the derived eq 14, which permits the results to be

$$\log k_2 = \rho[\sigma_p^+ + 0.60(\sigma_m^+ + 0.08D - 0.084)] + C \quad (14)$$

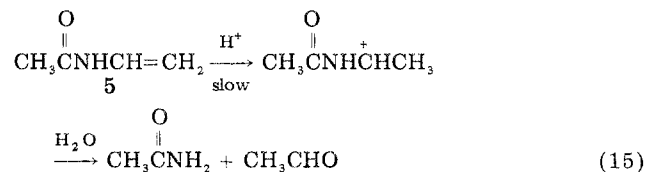
plotted on the same graph used for the 1,1-disubstituted cases, is shown in Figure 2.

Vinyl halides are a challenging group of compounds for which rates were not available when our initial correlation was made. Halogens are net electron withdrawers in electrophilic reactions, but, as mani-

fested in the σ_m^+ and σ_p^+ parameters for chloro of 0.40 and 0.11, donate electrons by resonance. We have now measured the rates of two members of this class, 2-chloro-1,3-butadiene and 2-bromopropene,²² and the correlation passes this test, as shown by the excellent fit (Figure 2) of these rates.

Vinyl esters provided the impetus for our initial studies, but electrophilic substituent parameters for acyloxy groups, determined by the defining reaction, cumyl chloride solvolyses, were not available. Our determination of these σ_p^+ constants as -0.06 (for AcO) and -0.14 (for $(\text{EtO})_2\text{PO}_2$) allows the rates of 17 representatives of this class to be included in Figure 2.²⁵ Two of these compounds, $(\text{EtO})_2\text{PO}_2\text{C}(\text{c-Pr})=\text{CH}_2$ and $(\text{EtO})_2\text{O}_2\text{PC}(\text{OEt})=\text{CH}_2$, deviate noticeably below the line in Figure 2. A satisfactory explanation of these deviations is not yet available, but it is possible that steric effects, "the last refuge of the puzzled organic chemist",²⁶ may play a role. All of the substituents present in these particular derivatives, namely EtO, c-Pr, and $(\text{EtO})_2\text{PO}_2$, are rather large and, furthermore, have a conformational preference in stabilization of an adjacent positive charge. It is to be hoped that further developments will provide a more definitive basis for interpreting these results.

Vinyl amides (enamides) are a class of compounds whose electrophilic reactivity had not been examined, in contrast to the great deal of attention devoted to the related vinyl ethers and esters. The study of these compounds is also relevant for comparison with amide hydrolysis, a topic of great current interest.²⁷ We have now examined *N*-vinylacetamide (5)²⁸ and have found²⁹ that this compound undergoes hydration by the $A_{SE}2$ route (eq 15) with a rate ($k_{\text{obsd}}/[\text{H}^+] = 3.75 \times 10^{-2} \text{ M}^{-1}$



s^{-1} in dilute HCl) close to that predicted by eq 9 (Figure 2), using the reported σ_p^+ value (-0.61)¹⁷ for this group.

Ethylene is the simplest possible alkene and may be regarded as the parent of all the others. The only previously measured rates of protonation of this compound in aqueous acid were at 170–190 °C at 100 bars pressure.³⁰ We have been able to measure rates at 25 °C in 76–84% H_2SO_4 with an excellent correlation of $\log k$ by H_0 with slope -1.54 .³¹ These data overlap the range of acidity for which rates were measured for *p*-nitrostyrene,^{7d} and at $H_0 = -7.37$ ethylene is less reactive by a factor of only 24. The substituent con-

(25) S. Y. Attia, J. P. Berry, K. M. Koshy, Y.-K. Leung, E. P. Lyznicki, Jr., V. J. Nowlan, K. Oyama, and T. T. Tidwell, *J. Am. Chem. Soc.*, **99**, 3401 (1977).

(26) Quoted from a 1941 textbook by H. C. Brown, "Boranes in Organic Chemistry", Cornell University Press, Ithaca, N.Y., 1972, p 56.

(27) (a) R. Wolfenden, *J. Am. Chem. Soc.*, **98**, 1987 (1976); (b) B. G. Cox and A. E. A. Porter, *ibid.*, **98**, 159 (1976); (c) R. Breslow and D. E. McClure, *ibid.*, **98**, 258 (1976); (d) J. H. Smith, *ibid.*, **98**, 3598 (1976); (e) A. Williams, *ibid.*, **98**, 5645 (1976); C. J. O'Connor et al., *Aust. J. Chem.*, **29**, 307 (1976); *J. Chem. Soc., Perkin Trans 2*, 362, 369 (1976).

(28) D. J. Dawson, R. D. Gless, and R. E. Wingard, Jr., *J. Am. Chem. Soc.*, **98**, 5996 (1976).

(29) Unpublished results.

(30) B. T. Baliga and E. Whalley, *Can. J. Chem.*, **43**, 2453 (1965); **42**, 1019 (1964).

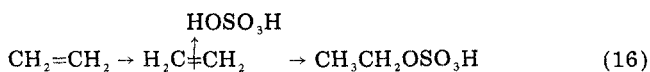
(31) W. K. Chwang, V. J. Nowlan, and T. T. Tidwell, *J. Am. Chem. Soc.*, in press.

(23) (a) P. Knittel and T. T. Tidwell, *J. Am. Chem. Soc.*, **99**, 3408 (1977); (b) T. Okuyama and T. Fueno, *J. Org. Chem.*, **39**, 3156 (1974), and preceding publications.

(24) J. Hine and N. W. Flachskam, *J. Am. Chem. Soc.*, **95**, 1179 (1973).

stant for *p*-nitrophenyl calculated by eq 12 is -0.02 , so eq 9 predicts ethylene to be less reactive by a factor of 2. The similarity of the predicted and observed rates of these quite different alkenes represents a significant confirmation of the validity of the rationale of eq 9.

An excellent recent textbook of organic chemistry has proposed that the mechanism of ethylene protonation in 98% H_2SO_4 "almost certainly does *not* involve the primary carbonium ion" but reacts via a π -complex route (eq 16).³² Our results indicate that ethylene



protonates by the same route as the other alkenes, namely through an $\text{A}_{\text{SE}2}$ transition state which presumably leads to an open ethyl carbonium ion (eq 17).



If the π complex intervened, it would be implied that the transition state leading to the π complex was stabilized relative to the $\text{A}_{\text{SE}2}$ transition state, and, therefore, ethylene would be expected to be more reactive than predicted by eq 9. In fact, ethylene is somewhat less reactive than expected relative to *p*-nitrostyrene. Because of its steep acidity dependence, the ethylene rate extrapolated to $H_0 = 0$ is decreased by a further substantial factor relative to *p*-nitrostyrene. This extrapolated ethylene rate is included in Figure 2 and deviates well below the correlation, but we do not believe the low rate is an accurate reflection of the reactivity of this compound. The similarity of the rate to *p*-nitrostyrene within the range of experimental observation is a much more realistic comparison.

Further support for ethylene having the same reaction mechanism as the other alkenes comes from the work of Baliga and Whalley,³⁰ who report that in the series $\text{CH}_2=\text{CH}_2$, $\text{MeCH}=\text{CH}_2$, and $\text{Me}_2\text{C}=\text{CH}_2$ the activation entropies and volumes are similar, but there is a monotonic decrease in activation enthalpy with increasing methyl substitution.

It may be argued that the intermediate in ethylene protonation is a π complex even though the transition state is that of the $\text{A}_{\text{SE}2}$ mechanism. However, such a bridged intermediate would further complicate the mechanism and would require convincing experimental justification. It has also been argued^{14c} that protonation of alkenes, including ethylene, involves a bridged transition state leading to an open intermediate. We believe our kinetic results indicate otherwise. Another possibility is attack of solvent forming a covalent bond at the α carbon, concerted with protonation at the β carbon, and while this cannot be excluded, we have no convincing evidence that it occurs.

The preferred geometry of the ethyl cation, as calculated by different theoretical treatments, has varied over the years, but the most recent results favor the bridged structure in the gas phase by 6–9 kcal/mol.³³

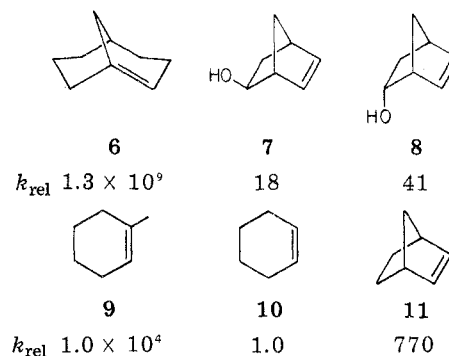
(32) A. Streitwieser, Jr., and C. H. Heathcock, "Introductory Organic Chemistry", Macmillan, New York, N.Y., 1976.

(33) (a) L. Radom, D. Poppinger, and R. C. Haddon, *Carbonium Ions*, 5, 2303 (1976); (b) D. Heidrich, M. Grimmer, and H.-J. Köhler, *Tetrahedron*, 32, 1193 (1976); (c) D. Heidrich and M. Stromeyer, *Z. Chem.*, 16, 152 (1976); (d) W. A. Lathan, L. A. Curtiss, W. J. Hehre, J. B. Lisle, and J. A. Pople, *Prog. Phys. Org. Chem.*, 11, 175 (1974); (e) W. L. Jorgensen and J. E. Munroe, *Tetrahedron Lett.*, 581 (1977); (f) W. L. Jorgensen, *J. Am. Chem. Soc.* 99, 280 (1977); (g) I. Hirono, O. Kikuchi, and K. Suzuki, *Bull. Chem. Soc. Jpn.*, 49, 3321 (1976).

However, when solvation is taken into account, the open structure is favored by 14 kcal/mol.^{33e} While the temporal variations in the calculated energy differences require the magnitudes of these quantities to be viewed with skepticism, it is safe to conclude that the theoretical studies are consistent with the presence of an open ion in solution. Recent experimental work also does not exclude this possibility.³⁴

Direct observation of stable ions has been utilized to establish the structure of a great many cations in solution and, in particular, has been applied to the problem of differentiating bridged and open ions.^{14c} So far, the ethyl cation has eluded detection by NMR but remains a goal of great interest. One valuable conclusion that has emerged from these studies is that there is a "continuum" of ion structures possible, with a continuous variation in the degree of electron delocalization.³⁵ Indeed, this is an inevitable result derived from molecular orbital theory. However, we believe that our evidence on kinetics of alkene protonations shows that these transition states involve an unsymmetrical attack on the double bond to produce an ion similar in structure to an open ion.

Cyclic olefins have recently attracted interest, and greatly accelerated protonations of strained bridgehead olefins such as bicyclo[3.3.1]non-1-ene (6), relative to



an acyclic analogue, have been reported.³⁶ Rates of hydration of the epimeric 2-norbornen-5-ols 7 and 8 have recently been observed,³⁷ and we have measured the rates of 1-methylcyclohexene (9), cyclohexene (10), and norbornene (11) for comparison.³¹ These rates show a substantial rate retardation by the inductively electron-withdrawing hydroxyl groups in 7 and 8 and rate accelerations of 1.3×10^5 for 6 relative to 9 and 770 for 11 relative to 10.

The high reactivity of 6 has been attributed to the high ground-state strain of this alkene.³⁶ However, ground-state strain is not necessarily reflected in high rates of protonation, as illustrated by the fact that the highly strained^{38a} 1-methylcyclobutene has a lower rate of hydration than 1-methylcyclohexene.^{38b} It could also

(34) (a) M. Siskin, *J. Am. Chem. Soc.*, 98, 5413 (1976); (b) I. L. Reich, A. Diaz, and S. Winstein, *ibid.*, 91, 5635, 5637 (1969); (c) P. C. Myhre and K. S. Brown, *ibid.*, 91, 5639 (1969); (d) P. C. Myhre and E. Evans, *ibid.*, 91, 5641 (1969).

(35) G. A. Olah and P. R. Clifford, *J. Am. Chem. Soc.*, 95, 6067 (1973).

(36) Y. Chiang, A. J. Kresge, and J. R. Wiseman, *J. Am. Chem. Soc.*, 98, 1564 (1976).

(37) M. Lajunen and P. Hirvonen, *Finn. Chem. Lett.*, 245 (1974); these authors have recently reported a rate for 11 in HClO_4 that is consistent with ours (*ibid.*, in press). A rate ratio for 11/10 of 600 has been reported for proton-catalyzed addition of acetic acid: R. M. G. Roberts, *J. Chem. Soc., Perkin Trans 2*, 1183 (1976).

(38) (a) R. B. Turner, P. Goebel, B. J. Mallon, W. von E. Doering, J. F. Coburn, Jr., and M. Pomerantz, *J. Am. Chem. Soc.*, 90, 4315 (1968); (b) P. Riesz, R. W. Taft, Jr., and R. H. Boyd, *ibid.*, 79, 3724 (1957).

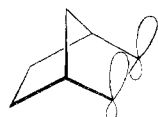
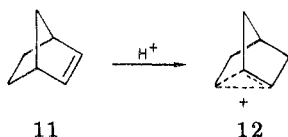


Figure 3.

be proposed that the high rate of norbornene reflects formation of a stabilized nonclassical norbornyl cation (12).



The question of bridging in norbornyl cations has been a topic of great interest over a long period of time, and recent publications have claimed to confirm this phenomenon under stable ion conditions^{39a} and in solvolysis.^{39b} However, extensive experimental work^{40a} and a recent theoretical treatment^{40b} argue against the importance of bridging in the norbornyl cation, and there will surely be more studies devoted to this system.

The fact that electrophilic additions to norbornenes lead to substantial amounts of unrearranged addition products argues strongly against the intervention of bridging in the transition states for these additions.⁴¹

(39) (a) G. A. Olah, *Acc. Chem. Res.*, **9**, 41 (1976); (b) H. Maskill, *J. Am. Chem. Soc.*, **98**, 8482 (1976).

(40) (a) H. C. Brown, *Acc. Chem. Res.*, **6**, 377 (1973); *Tetrahedron*, **32**, 179 (1976); (b) M. J. S. Dewar, R. C. Haddon, A. Komornicki, and H. Rzepa, *J. Am. Chem. Soc.*, **99**, 377 (1977).

(41) H. C. Brown and J. H. Kawakami, *J. Am. Chem. Soc.*, **97**, 5521 (1975).

We attribute some of the high reactivity of 11 to the unsymmetrical distortion of the molecule, so that the lobes of the p orbitals on the exo face of norbornene contain excess electron density and are vulnerable to electrophilic attack (Figure 3). This argument is supported by theoretical studies.⁴²

Recalculation of the correlation appeared desirable because of the greatly increased number of reactivities available since the correlation was formulated. We have tested eq 9 with a set of 29 of the alkenes whose rates seemed to us most reliable using a revised value of σ_p^+ of -0.83 measured by us²⁹ for EtO. This gave a correlation coefficient of 0.980 with $\rho = -10.7$ and $C = -8.96$. When all of the 96 points were included, the corresponding values were 0.938, -10.5 , and -8.92 , respectively. Thus, the correlation line defined by all the points was essentially the same as that determined by the selected points but with more scatter in the former case. The group of selected points consisted of those 1,1-disubstituted compounds for which reliable rate constants measured in water were available, excluding substituted styrenes, hydrocarbons with steep acidity dependences, and crowded phosphates. Many other substituents remain to be tested, but so far eq 9 appears to be a reliable guide to the rates and mechanism of alkene hydrations.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the National Research Council of Canada for support of this work.

(42) S. Inagaki, H. Fujimoto, and K. Fukui, *J. Am. Chem. Soc.*, **98**, 4054 (1976).

Preferential Solvation and the Role of Solvent in Kinetics. Examples from Ligand Substitution Reactions

Cooper H. Langford* and James P. K. Tong

Metal Ions Group, Chemistry Department, Carleton University, Ottawa, Canada

Received November 29, 1976

In the kinetic literature, an embarrassing ambiguity has plagued many distinguished authors. When a reaction seems to demand participation of a solute and a solvent molecule in a way parallel to bimolecular gas-phase reaction, the question arises: can a second-order rate constant be calculated by dividing an observed first-order rate constant by the molar concentration (or the activity) of the solvent?

Such second-order rate constants are frequently calculated, but the authors usually express some malaise. This malaise arises from the fact that a careful

analysis of the concept of molecularity and its scope and limits for solution have not yet been finally given. This Account will support the claim¹ that such second-order solvolysis rate constants are not useful. The problem just described is not a minor matter. It is symptomatic of a lack of clarity concerning some fundamental aspects of solution kinetics.

Similarly, *mixed solvent* studies in kinetics do not readily clarify hypotheses concerning the mechanistic role of one solvent component. At risk of a bad pun, mixed solvents are a kineticist's troubled waters. Nonetheless, for practical and theoretical reasons, mixed solvents continue to be widely used. They are, after all, of synthetic and even industrial significance.

Our present purpose is to examine certain concepts and to discuss experiments that clarify the issues indicated above. No claim is made that all the difficulties

Cooper H. Langford was born at Ann Arbor, Mich., in 1934. He holds an A. B. degree from Harvard and a Ph.D. from Northwestern. He has taught at Amherst College and as a visitor at Columbia. He is now settled in Canada and has been Professor of Chemistry at Carleton University since 1967. James P. K. Tong was born in Hong Kong in 1947. He was awarded an honors B.Sc. at McGill in 1969. He completed his Ph.D. at Carleton in 1974 and is presently a postdoctoral fellow at McMaster University. Drs. Langford and Tong are interested in reaction mechanisms in inorganic chemistry and inorganic photochemistry as well as NMR studies of solvation.

(1) C. H. Langford, *J. Chem. Educ.*, **46**, 577 (1969).