Entropy of Activation of Reactions Involving Rate-Determining Proton Transfer to Carbon

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The entropy of activation has been a useful criterion in distinguishing between A-1 and A-2 mechanisms of acid-catalyzed reactions.[1,2] The interpretation of $\Delta S^{\ddagger}$ for reactions in which rate-determining protonation of an unsaturated carbon atom is a mechanistic possibility, however, has not been discussed in detail. The purpose of this Note is to suggest a correlation, based on available experimental data, between free energy and entropy of activation for reactions in which the A-SE2 mechanism is operative.

Since transition-state theory is basically an equilibrium theory of kinetics, $\Delta G^{\ddagger}$ and $\Delta S^{\ddagger}$, like ΔG° and ΔS°, must be based on a standard state in order to be compared and interpreted. For bimolecular reactions, it is conventional to do this by computing them from the second-order rate constant, establishing the standard state as 1 M concentration or unit activity. For acid-catalyzed reactions this frequently requires long extrapolation from rate data obtained in highly acidic media.

Recent research on the equilibrium protonation behavior of weak bases[3,4] and the acidity function behavior of different strong acids[5] shows that such extrapolations are uncertain. Furthermore, most acidity function data refer to 25°. Studies of H_0 in HCl, H_3PO_4,[6] and H_2SO_4[7] and of H_R in H_2SO_4[8] show that acidity functions are temperature dependent. The use of acidity function values for extrapolation of experimental data obtained at temperatures appreciably different from 25° is thus another source of error. Even when temperature-corrected acidity values are used, it is sometimes found that the slopes of log k *vs.* acidity function plots change with temperature. The resulting acidity dependence of the energy of activation introduces added uncertainty. Finally, the order of precision of much kinetic data itself leads to considerable uncertainty in values for activation parameters.[9]

Nevertheless, the wide range of $\Delta S^{\ddagger}$ values reported for A-SE2 reactions (Table I) seems indicative of something more than experimental uncertainty.

Consideration here has been confined to reactions carried out in aqueous acidic media (no more than 5% organic cosolvent) in which the initial and rate-determining step is slow protonation of an unsaturated carbon atom. Data for substrates of varying types are listed in Table I. At least one representative of each type has been shown to react according to the A-SE2 mechanism by its solvent deuterium isotope effect. In

TABLE I

ENTROPY OF ACTIVATION VALUES FOR A-SE2 REACTIONS AT 25°

Substrate	Log k_2[a]	$\Delta S^{\ddagger}$, eu	$\Delta H^{\ddagger}$, kcal/mole	Ref
Ethyl ethynyl ether	+2.52	−5	12	*b*
1-N-Morpholino-1-isobutene	+2.49	−4	13	*c*
Propyl ethynyl ether	+2.47	−1	14	*b*
Methyl ethynyl ether	+1.89	−10	12	*b*
Azulene	+0.50	−7	15	*d*
Ethyl vinyl ether	+0.26	−11	14	*e*
t-Butylthioethyne	−0.52	−1	18	*f*
Ethylthioethyne	−0.68	−6	17	*f*
2-Ethoxy-1-cyclopentene-1-carboxylic acid	−0.84	−15	14	*g*
1,3,5-Trimethoxybenzene-2-*t*	−1.21	−16	14	*h*
1-Ethylthio-1-butyne	−1.68	−6	18	*i*
1-(*t*-Butylthio)-1-propyne	−1.81	−4	19	*i*
Allylmercuric iodide	−1.85	−12	16	*j*
1-Ethylthio-1-propyne	−2.05	−4	19	*i*
Vinylmercuric iodide	−3.88	−17	18	*k*
Thiophene-2-boronic acid	−4.82	−26	17	*l*
m-Methylstyrene	−6.00	−28	17	*m*
Styrene (in sulfuric acid)	−6.44	−29	18	*m*
p-Methoxybenzeneboronic acid	−6.72	−20	21	*n*
p-Chlorostyrene	−6.85	−29	18	*m*
Styrene (in $HClO_4$)	−6.88	−25	20	*o*
p-Methyl-*cis*-stilbene	−7.64	−26	20	*p, q*
m-Chlorostyrene	−7.67	−27	20	*m*
Thiophene-3-boronic acid	−7.96	−23	23	*l*
p-Methyl-*p*′-nitro-*cis*-stilbene	−8.44	−32	20	*p*
p-Methylbenzeneboronic acid	−8.53	−32	20	*r*
cis-Stilbene	−8.62	−29	21	*p, q*
m-Methoxy-*cis*-stilbene	−8.86	−28	21	*p*
p-Chlorophenylpropiolic acid	−9.08	−23	23	*s*
m-Nitrostyrene	−9.35	−30	21	*m*
p-Fluorobenzeneboronic acid	−9.67	−26	21	*r*
cis-Cinnamic acid	−9.79	−21	25	*t*
Benzeneboronic acid	−9.97	−37	20	*r*

[a] Rate constant (l. mole^{-1} sec^{-1}) at $H_0 = 0$ or $[H^+] = 1.0\,M$; see text for discussion of extrapolation. [b] E. J. Stamhuis and W. Drenth, *Rec. Trav. Chim.*, **80**, 797 (1961). [c] E. J. Stamhuis and W. Maas, *J. Org. Chem.*, **30**, 2156 (1965). [d] B. C. Challis and F. A. Long, *J. Am. Chem. Soc.*, **87**, 1196 (1965). [e] A. J. Kresge and Y. Chiang, *J. Chem. Soc.*, in press. We are grateful to Professor Kresge for preprints of these papers. [f] W. Drenth and H. Hogeveen, *Rec. Trav. Chim.*, **79**, 1002 (1960). [g] T. H. Fife, *J. Am. Chem. Soc.*, **87**, 1084 (1965). [h] A. J. Kresge, private communication; A. J. Kresge and Y. Chiang, *ibid.*, **84**, 3976 (1962). We are grateful to Professor Kresge for making his data available to us prior to publication. [i] H. Hogeveen and W. Drenth, *Rec. Trav. Chim.*, **82**, 410 (1963). [j] M. M. Kreevoy, P. J. Steinwand, and W. V. Kayser, *J. Am. Chem. Soc.*, **88**, 124 (1966). [k] M. M. Kreevoy and R. A. Kretchmer, *ibid.*, **86**, 2435 (1964). [l] R. D. Brown, A. S. Buchanan, and A. A. Humffray, *Australian J. Chem.*, **18**, 1521 (1965). [m] J. P. Durand, M. Davidson, M. Hellin, and F. Coussemant, *Bull. Soc. Chim. France*, 43 (1966). [n] H. G. Kuivila and K. V. Nahabedian, *J. Am. Chem. Soc.*, **83**, 2159 (1961). [o] W. M. Schubert and B. Lamm, *ibid.*, **88**, 120 (1966). [p] F. B. Miles, Ph.D. Dissertation, University of California at Berkeley, 1964; *cf.* D. S. Noyce, D. R. Hartter, and F. B. Miles, *J. Am. Chem. Soc.*, **86**, 3583 (1964). [q] D. R. Hartter, Ph.D. Dissertation, University of California at Berkeley, 1964. [r] K. V. Nahabedian and H. G. Kuivila, *J. Am. Chem. Soc.*, **83**, 2167 (1961). [s] M. A. Matesich, Ph.D. Dissertation, University of California at Berkeley, 1966; *cf.* D. S. Noyce, M. A. Matesich, M. D. Schiavelli, and P. E. Peterson, *J. Am. Chem. Soc.*, **87**, 2295 (1965). [t] D. S. Noyce, P. A. King, F. B. Kirby, and W. L. Reed, *ibid.*, **84**, 1632 (1962).

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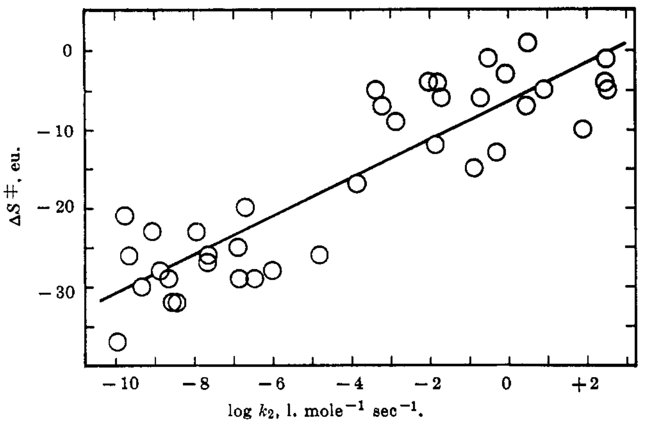

Figure 1.—Variation of the entropy of activation for rate-determining protonation of unsaturated carbon with the logarithm of the second-order rate constant at 25°.

most cases, additional evidence for this mechanism has been presented.

In many cases, activation parameters have been recalculated from rate data given in the references cited. Only those were included for which the acidity dependence of rates had been examined sufficiently to permit extrapolation to $H_0 = 0$ or $[H^+] = 1.0\ M$, whichever was convenient. These standard states certainly differ, but a more exact treatment is not warranted in view of the varied conditions under which reactions were studied. Temperature corrections for H_0[6,7] were applied where possible, a consistent set of H_0 values was used for H_2SO_4,[10,11] and rate constants were extrapolated to the standard state of acidity and 25° for calculation of $\Delta S^\ddagger$. It is estimated that most of the $\Delta S^\ddagger$ values listed have an uncertainty of several entropy units.

Figure 1 shows a definite trend to increasingly negative entropies of activation for less reactive compounds. The least-squares line, eq 1, fits the data with

$$\Delta S^\ddagger = 2.28 \log k_2 - 8.27 \qquad (1)$$

a standard deviation in $\Delta S^\ddagger$ of 5.00 eu. When the correlation is expressed in terms of the free energy of activation, eq 2, it can be compared with free energy–

$$\Delta S^\ddagger = -1.67 \times 10^{-3} \Delta G^\ddagger + 20.93 \qquad (2)$$

entropy correlations for protonation equilibria of primary aniline[7] and triarylcarbinol[8] bases in sulfuric acid. The slope reported here for entropy–free energy of activation, -1.67×10^{-3}, is in good agreement with the value of -1.5×10^{-3} found for equilibrium protonation of anilines. Both differ from the slope of -6.3×10^{-3} found for triarylcarbinol bases, and from the theoretical slope of -4.63×10^{-3} predicted by simple electrostatic theory for charging a sphere in a continuous dielectric medium.[8]

The complex variations observed in entropies and enthalpies of ionization of weak acids are not well understood.[12] The specific structural and solvation factors involved must also affect entropies of activation of acid-catalyzed reactions. In view of this, even qualitative agreement with the prediction of a simple electrostatic model for charging a spherical ion is somewhat surprising.

Two conclusions may be drawn from the correlation reported here. First, entropies of activation ranging from near zero to strongly negative values are consistent with the A-SE2 mechanism if there is a corresponding difference of several powers of ten in reactivity. Secondly, aniline base protonation is a better model than triarylcarbinol base protonation for this behavior.

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1-Alkyl-2-aryl-5-chloroimidazoles

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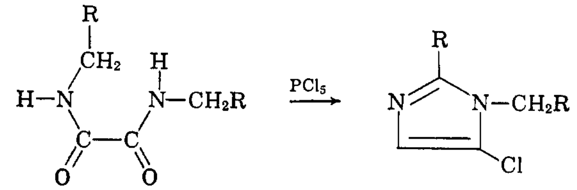
1-Methyl-5-chloroimidazole (IIa) and 1-ethyl-2-methyl-5-chloroimidazole (IIb) represent synthetically useful intermediates, having been employed as starting materials for the preparation of purines[1] and thiapurines.[2]

The method for synthesizing IIa and b, discovered by Wallach[3] and elaborated by Sarasin,[1a] involves the reaction of N,N′-dimethyl- and N,N′-diethyloxamide (Ia and b), *respectively*, with phosphorus pentachloride.



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IIa, R = H
b, R = CH_3

For many years this reaction was believed to be limited in scope to these two cases.[5] Recent publications by Kochergin[4] and by Trout[6,7] have extended the method to include the cyclization of a number of higher, symmetrical N,N′-disubstituted oxamides. Cyclization of the unsymmetrically substituted N-ethyl-N′-butyl-

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