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THE ENTHALPY-ENTROPY RELATIONSHIP AND ITS IMPLICATIONS FOR ORGANIC CHEMISTRY

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INTRODUCTION

Equilibrium and rate constants are conveniently expressed in terms of the standard free energy change and the free energy of activation, respectively.

$$RT \ln K = -\Delta F^{0} \qquad \text{Equation 1}$$

$$RT \ln k = -\Delta F^{\pm} + RT \ln \frac{\kappa \bar{k} T}{h} \qquad \text{Equation 2 (62a) (152)}$$

Free energies themselves are functions of the absolute temperature, the enthalpy and the entropy.

$$\begin{aligned} \Delta F^{0} &= \Delta H - T\Delta S^{0} \\ \Delta F^{\pm} &= \Delta H^{\pm} - T\Delta S^{\pm} \end{aligned} \qquad \text{Equations 3}$$

The latter two quantities may be considered to be independent of the temperature over the ranges used for most practical purposes. The effect of a change in structure or solvent on free energies is usually accompanied by an effect on both the enthalpy and the entropy. The way in which the structural or solvent change affects the free energy is therefore itself a function of the temperature. Unless the entropy is the same for two reactions, one of them may be the faster at one temperature but the slower at another temperature. Similarly for equilibria, one reaction may be the more complete at one temperature but the less complete at another temperature.

In a series of related reactions involving *moderate* changes in structure or solvent the enthalpies and entropies vary, but usually not independently. A large entropy usually goes with a large enthalpy and a small entropy with a small enthalpy. This is true whether the quantities are descriptive of equilibria or of rates. At times the correlation of enthalpy with entropy approaches the precision of a linear relationship *characteristic of that particular reaction series.* The purpose of this review is to discuss the scope and consequences of such relationships.

Although free energy, enthalpy, and entropy are fundamental quantities for those whose view of nature is a macroscopic one, from the point of view of statistical and quantum mechanics these are derivable quantities. Since relationships among derivable quantities are in principle themselves derivable, it is appropriate to justify our concern with such apparently secondary relationships in general before proceeding to a consideration of the enthalpy-entropy relationship itself. The logical status of organic chemistry is, in a way, similar to that of the life sciences from which it derives its name. Although it is widely believed that the laws of living organisms are derivable from the laws of chemistry and physics, in practice these biological laws are sought for directly rather than left for eventual derivation. There is a lesser, but still important, gap between organic chemistry and the fundamental ideas of potential energy and quantum statistics. The connecting link is experimentally the measurement of heat capacities from absolute zero to the reaction temperature or theoretically the calculation of partition functions. Neither of these is at present a practical undertaking for the reactions of complex organic molecules, especially for reactions in solution. Theories of organic chemistry must therefore be constructed from the experimentally accessible quantities of organic chemistry: the free energies of activation or equilibrium, available from experiments at a single temperature, or better, the enthalpies and entropies of activation or equilibrium available from experiments done at several temperatures. Only in special and relatively rare cases can it be shown that rate or equilibrium constants (free energies) change with structure or solvent in a way that is a precise function of changes in potential energies (64). There is therefore no simple and accurate connection between effects on rate and equilibrium constants and effects on potential energy quantities such as resonance energy and the energy of electron displacements. It should perhaps be emphasized that changes in enthalpy or enthalpy of activation are likewise not simple functions of potential energy quantities. The enthalpy and the free energy depend just as much on the kinetic energy of the molecule as does the entropy (64).

In spite of the lack of direct connection between the more fundamental but less observable potential energies and the observable thermodynamic quantities, there are simple relationships between variations in the latter and variations in the structure of organic molecules. One of the most important of these, a linear free energy relationship, is the well-known Hammett equation (64). The Hammett equation is derivable from a linear potential energy relationship if the entropy of activation is constant (64, page 119). On the other hand it is known empirically to apply to reactions that contravene the constant-entropy conditions of that derivation. That is, it works for reactions in which the effects of structural changes on the free energy are not due entirely to potential energy changes. In practice, then, the Hammett equation is partly empirical and its success justifies the search for other relationships among thermodynamic quantities and between thermodynamic quantities and structural parameters. In fact, the Hammett equation seems to apply to reactions in which the entropy is variable only in those cases where the enthalpy is a linear function of the entropy (79). The converse is not true since the linear relationship between enthalpy and entropy is also encountered in reactions to which the Hammett equation does not apply, for example in aliphatic reactions. The enthalpy-entropy relationship should be of help in the eventual resolution of an important difficulty of free-energy relationships applied to systems of variable entropy: the free energies of such systems are functions of the temperature and so, therefore, are the relationships themselves. This is a problem that must be considered seriously in generalizing about the effect of structure or solvent on reactivity, because such effects can change not only in relative magnitude but even in sign as the temperature is changed.

THE ISOKINETIC TEMPERATURE

It has long been realized that changes in structure or solvent usually change both the enthalpy and the entropy of activation and that large values of $\Delta H^{\pm}$ tend to accompany large values of $\Delta S^{\pm}$; similarly for ΔH and ΔS (60, 143, 36, 85a, 16, 74). At times this tendency attains the precision of a linear relationship between $\Delta H^{\pm}$ and $\Delta S^{\pm}$ or ΔH^0 and ΔS^0 (60, 143, 36, 74). *Not all reaction series exhibit the linear relationship even approximately and one of the purposes of this review is to show the scope of application of the relationship insofar as the current available data allow.* A number of examples show only a trend, yet there are enough such trends to make coincidence unlikely and to suggest that they represent the linear relationship partly obscured by some superimposed independent variation of the enthalpy or entropy. For purposes of discussion the relationship may be defined by the linear equation:

$$\Delta H^{\pm} = \Delta H_0^{\pm} + \beta\Delta S^{\pm}. \qquad \text{Equation 4}$$

In equation 4, $\Delta H_0^{\pm}$ is simply the intercept or value of $\Delta H^{\pm}$ corresponding to $\Delta S^{\pm} = 0$. It will usually have no physical meaning. The slope of the relationship is β, a quantity having the dimensions of absolute temperature. The free energy of activation, which determines the rate at any temperature, is given by

$$\Delta F^{\pm} = \Delta H^{\pm} - T\Delta S^{\pm} \qquad \text{Equation 5}$$

Combination of equations 4 and 5 gives:

$$\Delta F^{\pm} = \Delta H_0^{\pm} - (T - \beta)\Delta S^{\pm} \qquad \text{Equation 6}$$

When $T = \beta$, $\Delta F^{\pm} = \Delta H_0^{\pm}$ and all the rate or equilibrium constants are the same within the precision of the relationship. Hence β is called the *isokinetic* or *isoequilibrium* temperature and equation 4 the isokinetic relationship. Of course if β is extremely far from the usual working temperature the relationship may be invalidated by changes in $\Delta H^{\pm}$ with temperature. In that case β is merely a slope and has no physical meaning.

It is clear from the possible existence of an isokinetic temperature that certain precautions should be taken in the interpretation of the effect of structure or solvent changes on the rate of a reaction. Because the temperature chosen might be close to the isokinetic temperature it is not safe to conclude from the constancy of the rates that the changed structure or nature of the solvent has no effect. An example is the impression that solvation is of no importance in free radical reactions. While this seems to be true for some radical reactions it is not true in general. The decomposition of phenylazotriphenylmethane in a series of solvents goes at nearly the same rate in all of them at about 36°. But experiments at a number of temperatures reveal a statistically significant 4 to 5 kilocalorie change in $\Delta H^{\pm}$, sufficient to cause a 1600-fold change in rate were it not for the compensating entropy change (92).

THE HAMMETT EQUATION AND THE ISOKINETIC TEMPERATURE

The Hammett equation (equation 7) relates the logarithms of the rate constants of aromatic side chain reactions to structural parameters. It is therefore a linear relationship between free energies of activation and structural parameters.

$$\log k/k_0 = \rho\sigma \qquad \text{Equation 7 (64, 79)}$$

In the Hammett equation σ is a constant characteristic of the *meta* or *para* substituent on the benzene ring while ρ is a constant characteristic of the reaction at the side chain. The Hammett equation is also a linear relationship of *potential* energies if the kinetic energy and entropy contributions to the free energy change cancel out or can be neglected. If the entropies of activation are the same for both reagents, it can be assumed that the kinetic energies are also the same. The requirement for the applicability of the Hammett equation as a *potential energy* relationship is therefore that the entropies of activation of the reactions be the same (64). In most of the reactions for which the Hammett relationship is successful the entropies of activation are not in fact known. In the few cases where the entropy is known it usually varies and in such a way that the enthalpy and entropy are linearly related. By combining equations 4 and 5 it follows that

$$\Delta F^{\pm} = (T/\beta)\Delta H_0^{\pm} + (1 - T/\beta)\Delta H^{\pm} \qquad \text{Equation 8}$$

The Hammett equation can therefore be regarded as a linear enthalpy relationship even in those cases where the entropy is variable. It is possible, but it must be emphasized, not proven, that in such cases the enthalpies are proportional to potential energies which would make even the extended Hammett equation a linear potential energy relationship. From equation 8 it can be seen that at temperatures above β, increments in $\Delta H^{\pm}$ produce decrements in $\Delta F^{\pm}$ while at temperatures below β the reverse is true. Hence ρ must reach zero and change its sign at $T = \beta$. This being the case it is inadvisable to draw mechanistic conclusions from the sign of ρ unless ρ itself is very large.

An example of the approach of ρ to zero as the temperature approaches the isokinetic temperature is given by the ρ values for the decomposition of *para*-substituted *tert*-butyl perbenzoates in diphenyl ether (11). Although the extrapolation is of insufficient precision for a prediction of the isokinetic temperature from the observed change in ρ, the value of the isokinetic temperature taken from the $\Delta H^{\pm}$ *versus* $\Delta S^{\pm}$ plot is consistent with the trend in ρ values. The ρ values increase non-linearly from -0.90 to -0.52 as the temperature is raised from 100° to 131° (79). The isokinetic temperature is about 210°.

Near the isokinetic temperature there will still be variations in rate constant, but these will be due more to the apparently random deviations from a perfect isokinetic relationship than to the distance of the experimental temperature from the actual isokinetic temperature. Such variations in rate constant as do persist near the isokinetic temperature will usually not be well correlated by the Hammett equation. A correlation coefficient closer to unity then is obtained if $\Delta H^{\pm}$ rather than $\Delta F^{\pm}$ is plotted against *sigma* in such cases. In different statistical terms the connection between the scatter about the Hammett equation line and the scatter about the isokinetic relationship line may be stated as follows: the standard deviation of the experimental enthalpy of activation from that predicted by the isokinetic relationship is about the same number of calories per mole as the free energy difference corresponding to the standard deviation of the experimental log k from that predicted by the Hammett equation. It may therefore be that the same factors, other than experimental error, are to blame for deviations from both relationships.

THE CORRELATION OF REACTIONS BY MEANS OF THE ISOKINETIC RELATIONSHIP

One of the limitations and yet one of the useful features of the isokinetic relationship is that it can be expected to apply only to a series of reactions in which the solvent or structural change does not change the mechanism of the reaction or the nature of the transition state. The existence of the relationship is evidence favoring a constant mechanism for the related series of reactions.

It is frequently considered that a striking change in activation energy or enthalpy necessarily means a change in mechanism. This can be a mistake. Equally unreliable is the idea that identity of activation enthalpy or identity of activa-

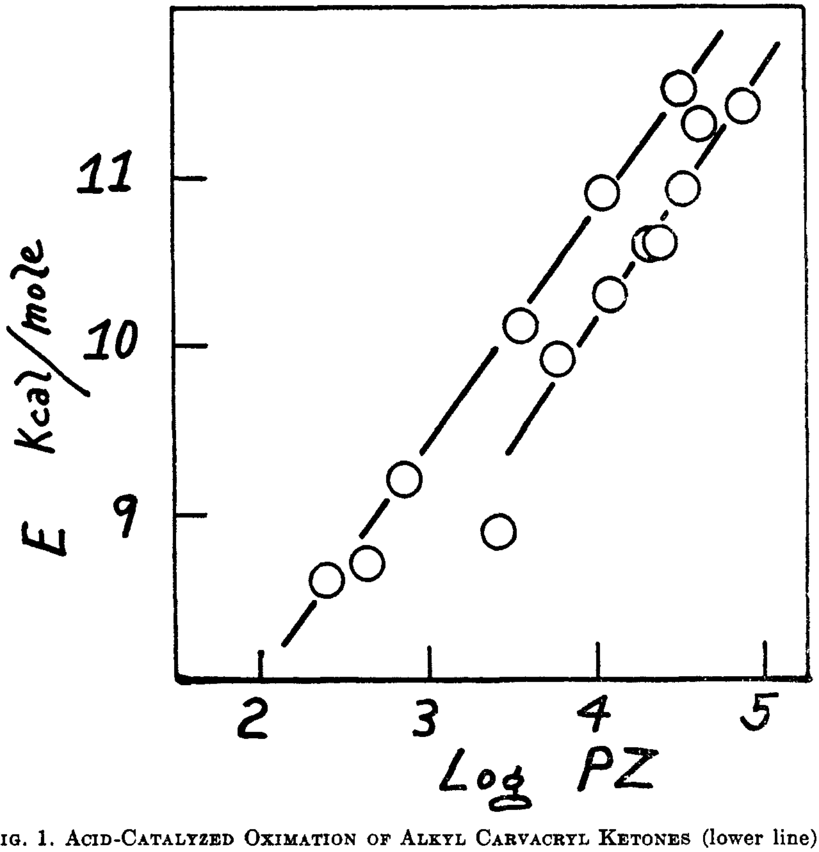
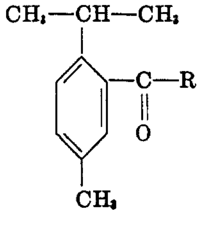


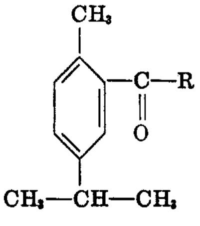
Fig. 1. Acid-Catalyzed Oximation of Alkyl Carvacryl Ketones (lower line) and Alkyl Thymyl Ketones (upper line). The Isolated Point is Methyl Thymyl Ketone.

tion entropy (although not both at the same time) means that the mechanism is unchanged. It is probably not significant to compare the activation enthalpies of individual reactions as a criterion of mechanism: what is significant is any deviation from the isokinetic line. The range of activation enthalpies and entropies covered by a single isokinetic relationship is frequently quite large. A reaction of entirely different mechanism may well have an activation enthalpy corresponding to that of a point on the line but an activation entropy corresponding to that of an entirely different point on the line.

In Figure 1, for example, the upper line shows a linear relationship between the activation energy and log PZ (corresponding to activation enthalpy and entropy) for the addition of hydroxylamine to a series of alkyl thymyl ketones (37). Markedly displaced below and to the right of the line is the point for methyl thymyl ketone, the only member of the series with a significantly reduced steric hindrance and very likely a qualitatively different ground or transition state. Note, however, that neither the energy nor the log PZ of this compound is in any way abnormal. The energy of activation is like that of the *n*-heptyl compound while the entropy is like that of the *n*-butyl compound. The points related by the lower line of Figure 1 are for the oximation of alkyl carvacryl ketones; since they are less hindered their behavior is like that of methyl thymyl ketone.



Thymyl ketones



Carvacryl ketones

Another example is furnished by the well-known division of *cis-trans* olefin isomerizations into high entropy and low entropy categories, the latter presumably having a non-adiabatic mechanism and hence a lower "entropy" (96). This interpretation is an attractive one in general but seems unlikely to be true for the particular case of substituted stilbenes (31). The activation entropies for the latter reaction (Figure 2) are spread out over a nicely graded series and are linearly related to the activation energies. This indicates a single mechanism for the series.

The isokinetic relationship for structural changes is predicted by theory, although only with the aid of limiting assumptions. One such case, discussed by Hammett, is that of a reaction in which the only important change in free energy is electrostatic (64, page 84). The free energy then is expected to be proportional to the reciprocal of the dielectric constant and the enthalpy and entropy are linearly related. Other special cases in which structural changes, by influencing the solvation, might lead to the linear relationship are similar to those discussed below in which the solvent rather than the structure is the variable.

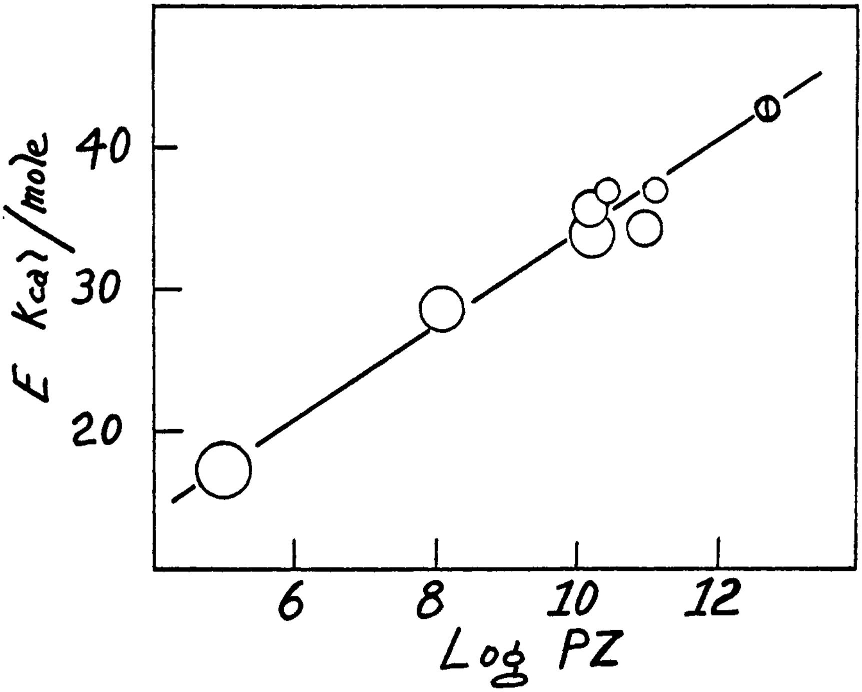


FIG. 2. EFFECT OF SOLVENT AND STRUCTURAL CHANGES ON THE STILBENE *cis-trans* ISOMERIZATION. THE SHADED POINT IS FOR THE UNSUBSTITUTED COMPOUND IN THE GAS.

STERIC HINDRANCE

Moderate changes in the degree of steric hindrance often do not remove a reaction from its isokinetic line but merely move it to a new location on the same line, as illustrated by the reaction of Figure 1. With a considerable increase in steric hindrance in the transition state a combined increase in enthalpy of activation and decrease in entropy of activation is to be expected. Such points lie above and to the left of the isokinetic line for the other reactions. Similarly, an unusually low degree of steric hindrance in the transition state may displace the point below and to the right of the line. Although a continuous series of lines corresponding to continuously varying degrees of steric hindrance might be expected, it is usually not observed. Apparently a critical degree of steric hindrance once surpassed initiates a new isokinetic series corresponding to a qualitatively different transition or ground state. An exception is the reaction of alkyl pyridines with ethyl iodide (24a). If desolvation of the ground state is a feature of the activation process, steric hindrance in the ground state might produce a series displaced towards lower enthalpies of activation for a given entropy. This may be the explanation of the dual lines in the case of the unimolecular decomposition of *meta* and *para* substituted benzoyl peroxides (upper line) and *ortho* substituted benzoyl peroxides (lower line, Figure 3) (12).

A possible explanation of discontinuous effects of steric hindrance may be the

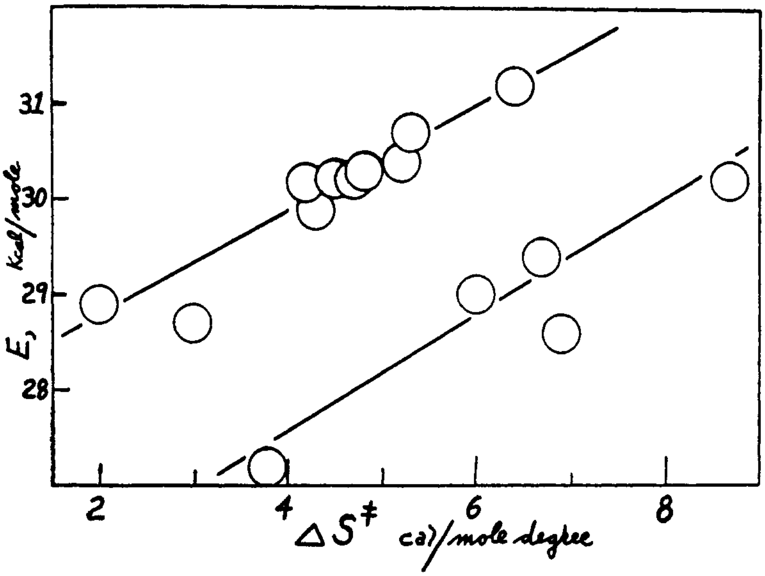


FIG. 3. DECOMPOSITION OF SUBSTITUTED BENZOYL PEROXIDES IN ACETOPHENONE. Upper line, *meta* and *para* substituted. Lower line, *ortho* substituted.

existence of double potential energy minima. Applied to the ground state this explanation says that there are two preferred molecular configurations and that a critical degree of steric hindrance makes the one that is ordinarily the more stable the less stable instead. In the case of an aromatic ketone the configurations might consist of the carbon-oxygen double bond oriented in the plane of the aromatic ring and, with steric hindrance, oriented perpendicular to the plane of the aromatic ring. Applied to the transition state, the two potential minima might consist of one in which the new bond is largely covalent and short and one in which the new bond is largely ionic and long, the latter being of lower potential energy only in the presence of a critical degree of steric hindrance to the formation of a short bond.

Other examples of the *ortho* effect are reactions 4 (note 4), 9a, 10, 12 (note 11), 48, and 49 of Table I.

SOLVENT CHANGES

Solvent changes often alter the enthalpy and entropy of activation of a reaction. If the solvents in a series perform closely similar roles in the reaction, it is expected, and often found, that the enthalpy of activation is a linear function of the entropy of activation. In some reactions solvents fall into two qualitatively different classes and the activation parameters fall on two lines rather than on a single one. An example is the decomposition of triethylsulfonium bromide in hydroxylic solvents (upper line of Figure 4) and in non-hydroxylic solvents (lower line) (100, page 278). The point mid-way between the two lines is for a mixture of toluene and benzyl alcohol, but mixtures with smaller amounts of

TABLE I

DATA ON ALL KNOWN REAL OR APPARENT ISOKINETIC RELATIONSHIPS

Reaction	Ref.	Notes	Energy Parameter	Entropy Parameter	β °K	$\bar{T}$ °K	n[a]	r[a]
1. Saponification of alkyl acetates and thiolacetates in 62% acetone.	103, 123, 107	*1*	$\Delta H^{\pm}$ 10 to 19	$\Delta S^{\pm}$ −33 to −6	270	280	13	0.982
2. Acid-cat. hydrolysis of alkyl acetates in 62% acetone.	103, 123, 107	*2*	$\Delta H^{\pm}$ 15 to 23	$\Delta S^{\pm}$ −27 to −6	330	320	7	.997
3. Acid-cat. hydrolysis of alkyl thiolacetates in 62% acetone.	103, 123, 107	*3*	$\Delta H^{\pm}$ 16 to 20	$\Delta S^{\pm}$ −32 to −19	330	320	7	.995
4. Acid-cat. hydrolysis of *p*-subst'd ethyl or methyl benzoates in aqueous ethanol, aqueous methanol, and aqueous acetone mixtures.	138	*4*	E 17.5 to 21	log PZ 6.3 to 8.1	440	370	19	.988
5. Saponification of methyl acetate in water, acetone-water, and ethanol-water.	60	*5*	E 10.45 to 15.00	log PZ 6.87 to 9.60	360	290	3	1.00
6. Saponification of valerolactone, phthalide, and 5- aminophthalide in aqueous-alcohol mixtures.	71	*6*	E 10.8 to 16.1	log PZ 7.4 to 10.6	380	290	9	.996
7. Saponification of ethyl benzoate in aqueous acetone, aqueous alcohol, aqueous dioxane, aqueous acetone-alcohol mixtures.	65, 60	*7*	E 12.9 to 19	log PZ 7.2 to 10.5	400	290	23	.995
8. Saponification of ethyl *m*-nitrobenzoate in aqueous acetone and aqueous alcohol.	65		E 13 to 16	log PZ 8.8 to 10.4	400	280	7	.997
9. Heterogeneous hydrolysis of ethyl carbonate on salts and metallic oxides.	124	*8*	E 11 to 63	log A 7 to 29	520	490	14	.990
9a. H^+-cat. esterification of *meta*- and *para*-subst'd benzoic acids in methanol.	67, 131	*9*	E 13.4 to 15.5	log PZ 5.9 to 7.6	260	310	13	.953
10. H^+-cat. esterification of *ortho*- subst'd benzoic acids in methanol.	67, 131	*9*	E 14.3 to 15.5	log PZ 6.0 to 7.2	260	310	4	.981

[a] Symbols: n = number of reactions; r = coefficient of correlation.

11. H^+-cat. esterification of *o*-, *m*-, *p*-substituted benzoic acids in cyclohexanol.	68, 69	*10*	E 17.4 to 20.0	log PZ 6.6 to 8.6	310	340	20	.944
12. Esterification of acids in alcohols as solvent without added catalyst. Unhindered combinations.	75	*11*	E 13 to 20.7	log PZ 2.5 to 5.7	540	420	8	.965
13. Esterification of straight chain acids in cyclohexanol, no added catalyst.	57		E 14.3 to 16.6	log PZ 2.8 to 4.3	400	400	7	.980
14. Esterification of acetic acid in equimolar mixtures with isobutyl alcohol as the pressure is increased.	114	*12*	E 16.48 to 18.78	log PZ 4.68 to 7.07	210	350	4	1.00
15. Reaction of methyl or ethyl iodide with tertiary aromatic amines in methanol.	27, 53, 148	*13*	E 14 to 23	log PZ 6.6 to 9.9	510	310	27	.977
16. *Meta* and *para*-substituted anilines with 2,4-dinitrophenyl halides in 99.8% ethanol.	34, 127	*14*	E 6 to 15	log PZ 2.4 to 5.6	550	310	16	.933
17. Methyl iodide with pyridine in alcohol-benzene mixtures.	59	*15*	E 14.9 to 18.0	log PZ 6.28 to 8.32	340	330	4	.999
18. Aniline with phenacyl bromide in various solvents.	36a	*16*	E 8 to 14	$\Delta S^{\pm}$ -56 to -28	210	310	6	.973
19. Pyridine or dimethylaniline with allyl bromide in various solvents.	76a	*16*	E 9 to 17.5	log PZ 2.4 to 8.4	300	300	7	.993
20. Acetolysis of cyclic tosylates and brosylates.	151	*17*	$\Delta H^{\pm}$ 23.5 to 30	$\Delta S^{\pm}$ -6 to $+7$	450	320	6	.961
21. Acetolysis of acyclic primary tosylates with no participating neighboring groups or neighboring phenyl.	150		$\Delta H^{\pm}$ 22.6 to 31.5	$\Delta S^{\pm}$ -20.9 to $+0.96$	400	360	4	.999
22. Acetolysis of brosylates with no neighboring groups.	150		$\Delta H^{\pm}$ 23.8 to 26.2	$\Delta S^{\pm}$ -8 to $+1.5$	310	330	4	.916
23. Solvolysis of tertiary iodides in 76% alcohol.	126	*18*	E 19.8 to 22.0	log PZ 12 to 13.2	470	300	9	.965
24. Alcoholysis of secondary alkyl chlorides in which the chlorine is *alpha* to a benzene ring.	3	*19*	E 20 to 25.5	log PZ 10.3 to 12	760	290	5	.960
25. Hydrolysis of *p*-nitrobenzyl bromide in aqueous dioxane mixtures.	63		E 15 to 19	$\Delta S^{\pm}$ -44 to -30	260	300	3	1.000

TABLE I—*continued*

Reaction	Ref.	Notes	Energy Parameter	Entropy Parameter	β °K	$\bar{T}$ °K	n^a	r^a
26. Reaction of ethyl arylsulfonates with sodium ethoxide in alcohol.	102		E 20.8 to 24.0	log PZ 11.7 to 15.3	185	310	5	.986
27. Hydrolysis of substituted benzoic anhydrides in 75% dioxane.	9		E 11 to 20	$\Delta S^\pm$ -40 to -28	750	340	9	.956
28. Hydrolysis of benzoyl chloride in aqueous acetone mixtures.	2, 136		$\Delta H^\pm$ 11 to 19	$\Delta S^\pm$ -41 to -7	200	290	6	.995
29. Solvolysis of substituted benzoyl chlorides in 60% ether-40% ethanol.	14		E 11 to 19	log PZ 5.5 to 9.5	450	280	8	.955
30. Solvolysis of substituted benzoyl chlorides in 95% acetone.	20		E 6.7 to 14.7	log PZ 2.1 to 5.9	460	290	5	.958
31. Hydrolysis of alkyl fructosides by aqueous acid.	72	*20*	E 25.2 to 29.4	log PZ 15.8 to 17.5	520	310	4	.980
32. Hydrolysis of alkyl glucopyranosides by aqueous acid.	72	*21*	E 31.5 to 35	log PZ 15.1 to 16.8	430	360	4	.996
33. Acid-catalyzed hydrolysis of disaccharides and oligo-saccharides with aldohexose part structure. One reducing fructoside is included, but three non-reducing fructosides fall off the line and were omitted.	100, p. 74		E 24 to 40	log PZ 11.3 to 20.4	360	330	10	.982
34. Acid-catalyzed hydrolysis of *p*-substituted benzamides.	98	*22*	E 22.0 to 24.6	$\Delta S^\pm$ -18.9 to -12.5	400	350	4	.984
35. Base-catalyzed hydrolysis of *p*-substituted benzamides.	98	*22*	E 16.1 to 18.9	$\Delta S^\pm$ -30 to -27	910	350	4	.960
36. *Ortho*-, *meta*-, and *para*-substituted phenyl sulfate hydrolysis.	28	*23*	E 23.6 to 28.4	log PZ 12.5 to 14.8	510	330	23	.970
37. Acid-catalyzed oximation of alkyl carvacryl ketones.	37	*24*	E 9.9 to 11.4	log PZ 3.80 to 4.89	300	310	7	.978
38. Acid-catalyzed oximation of alkyl thymyl ketones.	37	*24*	E 8.6 to 11.5	log PZ 2.4 to 4.5	300	310	6	.986

39. Formation of semicarbazones from *para*-substituted acetophenones in 83% alcohol.	43		E 4 to 11	log PZ 1.2 to 6.8	280	310	5	.998
40. Acid-catalyzed racemization of α-methylbutyraldehyde in dioxane-water mixtures.	5	*25*	$\Delta H^{\ddagger}$ 0.3 to 26	$\Delta S^{\ddagger}$ −60 to +15	330	300	4	.995
41. Acid-catalyzed rearrangement of substituted 3-hydroxypentene-1-yne-4 in 60% ethanol, limited to structures with two substituents.	15		E 21 to 27.5	log PZ 12.7 to 16.2	440	310	10	.965
42. Formation of phenyl isocyanate from benzoyl azide in various solvents.	106		E 25.4 to 31.6	$\Delta S^{\ddagger}$ 10 to 24	380	340	14	.974
43. Acid-catalyzed rearrangement of substituted hydrazobenzenes.								
In 75–80% alcohol.	47		E 12 to 19.7	log PZ 5 to 11.5 (min^{-1})	260	280	4	.999
In 90–100% alcohol.	42, 47		10 to 20	6 to 12	350	280	8	.977
44. Decarboxylation of acetone dicarboxylic acid in water and in a series of alcohols.	147		E 21.5 to 26.5	ln PZ 29.5 to 37.5	340	320	7	.994
45. Picolinic acid decarboxylation in a series of solvents.	32	*26*	$\Delta H^{\ddagger}$ 30 to 50	$\Delta S^{\ddagger}$ −8 to +36	460	450	13	.998
46. Decarboxylation of monosubstituted malonic acids in water.	100, p. 287; 49	*27*	E 27.6 to 29.0	ln PZ 26.1 to 33.7	95	380	5	.985
47. Decarboxylation of mesitoic acids substituted in the 3-position in 83% sulfuric acid or phosphoric acid.	8		$\Delta H^{\ddagger}$ 16 to 27	$\Delta S^{\ddagger}$ −30 to +7	300	350	6	.935
48. Decay of thermochromic color, less-hindered dianthrones.	76	*28*	E 16 to 19	log PZ 11.5 to 15	210	220	4	.991
49. Decay of thermochromic color, more-hindered dianthrones and xanthylideneanthrone.	76	*28*	E 11.5 to 20	log PZ 10.5 to 18	250	220	5	.989
50. Decomposition of benzene diazonium chloride in alcohols.	142, 116	*29*	E 24.5 to 27.5	log PZ 14 to 16	300	310	8	.999

TABLE I—*continued*

Reaction	Ref.	Notes	Energy Parameter	Entropy Parameter	β °K	$\bar{T}$ °K	n^a	r^a
51. Decomposition of benzene diazonium chloride in water and in carboxylic acids.	142, 116	*29*	E 24 to 31	log PZ 13 to 18	300	310	5	1.000
52. Diels-Alder reaction of cyclopentadiene with benzoquinone or α-naphthoquinone, in various solvents, with or without acid or phenol catalysts.	144 58 145 122	*30*	E 0 to 13	log PZ 1 to >	410	300	25	.958
53. Dimerization of cyclopentadiene in various solvents, and in carbon tetrachloride with acid catalysts.	122 145 120 82		E 4 to 17.5	log PZ −2 to 7.5	330	310	11	.987
54. Dimerization of cyclopentadiene, no solvent, pressures from 1 to 4,000 atmospheres.	120		E 17.0 to 18.9	log PZ 6.4 to 9.3	70	290	8	.999
55. Elimination of HCl from the β isomer of benzene hexachloride in aqueous-alcohol mixtures.	38, 40	*31*	E 30.6 to 33.1	$\Delta S^{\pm}$ 18.9 to 27.0	320	310	7	.996
56. Dehydrohalogenation of chlorofumarate, chloromaleate, bromofumarate, and bromomaleate with sodium hydroxide in water and in 54.2% aqueous ethanol.	39		E 17.5 to 26.2	$\Delta S^{\pm}$ −19 to −1	470	340	8	.923
57. Dehydrohalogenation of *cis*-dihaloethylenes in methanolic sodium methoxide.	99	*32*	E 24.1 to 35.1	$\Delta S^{\pm}$ 14 to 22	1320	360	3	.999
58. Dehydrohalogenation of *trans*-dihaloethylenes in methanolic sodium methoxide.	99	*32*	E 29.0 to 35.8	$\Delta S^{\pm}$ −12 to +24	190	320	3	.981
59. *Cis-trans* isomerization of substituted stilbenes in the liquid phase without solvent, stilbene in the gas and liquid phases, and *p*-amino-*p'*-nitrostilbene in xylene.	31 96	*33*	E 17.2 to 42.7	log PZ 5.0 to 12.8	720	470	8	.985

60. Isomerization of *cis*-chlorobenzene diazocyanide in a series of solvents.	90		E 21.4 to 26.1	log PZ 12 to 15	350	310	8	.995
61. Isomerization of azobenzene in a series of solvents and substituted azobenzene in benzene.	89	*34*	E 22 to 27	log PZ 11 to 14	340	310	13	.976
62. Reaction of ferrous ion with hydrogen peroxide and with a series of hydroperoxides.	109		E 9.4 to 13.1	$\Delta S^{\pm}$ 10.77 to 20.95	380	300	7	.976
63. Mutarotation of glucose, equilibria, in methanol-water mixtures.	50a		ΔH -1.3 to $+3.2$	ΔS -4 to $+12$	310	300	4	.999
64. Oxidation of *p,p'*-dichlorobenzyl sulfide with substituted perbenzoic acids in toluene and in isopropyl alcohol.	111		$\Delta H^{\pm}$ 5.2 to 11.3	$\Delta S^{\pm}$ -34 to -16	340	230	7	.994
65. Decomposition of *para*-substituted *tertiary*-butyl perbenzoates in diphenyl ether.	11	*35*	E 35.8 to 41.3	ΔS 12.2 to 23.7	480	390	5	1.000
66. Radical decomposition of *meta*- and *para*-substituted benzoyl peroxides in acetophenone.	12	*36*	E 29 to 31.2	ΔS 2 to 6.4	530	350	10	.973
67. Decomposition of phenylazotriphenylmethane in cyclohexane and a series of aromatic solvents.	92	*37*	$\Delta H^{\pm}$ 24.5 to 29.0	$\Delta S^{\pm}$ -1.2 to $+13.4$	310	320		.999
68. Decomposition of azo-bis-cycloalkylnitriles of ring sizes 5, 6, 7, 8, 10.	110	*38*	E 25.9 to 35.4	$\Delta S^{\pm}$ 5.9 to 18.9	660	340	5	.973
69. Association equilibrium of α-benzoyl-β,β-diphenylhydrazyl free radical in various solvents.	144		ΔH -10.4 to -5.6	ΔS -22 to -10	360	240	4	.951
70. Formation of bisulfite ions by the decomposition of N,N-disubstituted aminomethanesulfonic acids in water.	134		E 18.5 to 23.8	log PZ 12.5 to 14.0	990	300	6	.934
71. Decomposition of triethylsulfonium bromide in hydroxylic solvents.	100 (p. 278)	*39*	E 31 to 36	ln PZ 33 to 40	330	360	7	.950
72. Decomposition of triethylsulfonium bromide in nonhydroxylic solvents.	100 (p. 278)	*40*	E 28.3 to 33.0	ln PZ 34.4 to 41.6	340	320	5	.999

TABLE I—*continued*

Reaction	Ref.	Notes	Energy Parameter	Entropy Parameter	β °K	$\bar{T}$ °K	n^a	r^a
73. Equilibrium of substituted diphenylselenium dibromide with diphenylselenium and bromine in carbon tetrachloride.	95		ΔH 9.7 to 14.4	ΔS^0 17 to 30	390	290	4	.945
74. Rearrangement of ethyl benzylhydroxytriazolecarboxylate in a series of solvents.	48		E 26.5 to 36	ln PZ 29 to 49	250	310	4	.991
75. Solution (solubility) of *ortho*-dinitrobenzene in a series of solvents.	56	*41*	ΔH 5 to 8	ΔS/R 2.8 to 4.5	890		10	1.000
76. Equilibrium of complex formation between 2,4-dinitrochlorobenzene and substituted anilines in absolute ethanol.	121a		ΔH −18 to −3	ΔS^0 −59 to −11	320	310	11	.998
77. Dissociation equilibrium of acetic acid dimer in various wet solvents and in the vapor.	1	*42*	ΔH 5.0 to 14.5	ΔS^0 7 to 28	450	310	7	.933
78. Ionization of benzoic acid and substituted benzoic acids, electron-withdrawing *meta* and *para* substituents only.	18	*43*	ΔH −.4 to +.3	ΔS^0 −18 to −14.7	240	300	5	.992
79. Ionization of primary and secondary *n*-alkyl amines.	52		ΔH −14.1 to −11.9	ΔS 1.3 to 9.5	270	300	6	.989

1. *Tert*-Butyl points for both the acetates and the thiolacetates are above the line and were omitted. *2*. Because of the tendency of saturated groups to bunch, the relationship has essentially three points. Note that the line is parallel to that of the thiol esters under the same conditions. *3*. Not bunched. Parallel to the line for the corresponding oxygen compounds. The point for the trityl compound was omitted because it has been shown that trityl-sulfur cleavage takes place. *4*. Two points for *o*-nitrobenzoate in aqueous acetone and aqueous ethanol are available and fall off the line for the *p*-derivatives and on the high activation energy side. The line connecting the two *ortho* points is approximately parallel to that of the *para* points. Two points for *meta*-nitro fall on the *para* line. *5*. Nearly parallel but at higher energies than reaction 6. *6*. A very approximate point for butyrolactone falls near the line but was omitted. *7*. Parallel, but at higher energies than reaction 8. *8*. Note that β is within the range of experimental temperature. *9*. The line for reaction 10 is above (energy) that of reaction 9a. The *o*-fluoro point falls on the *meta-para* line of reaction 9a probably because fluorine is a small atom. Two points, *ortho*-ethoxy and -methoxy fall below the *meta-para* line. These three points have been omitted from the r-calculation of reaction 10, the latter two on the basis that a special mechanism probably exists for them. *10.* The points for the *ortho* compounds scatter somewhat more than the *para*. *ortho*-Methoxy and -ethoxy are below the line and have been omitted as in reaction 10. *11.* Three hindered combinations, acetic acid-*tert*-butanol, benzoic acid-*tert*-butanol and mesitoic acid-benzyl alcohol are above the line and were omitted. Points for strong acids or with added mineral acid are below the line and scattered. *12.* Other alcohols also have a linear E *versus* log PZ but the slopes are different. *13.* Three nitro-substituted amines form a parallel line to the left, while 2,6-N,N-tetramethylaniline is by itself to the right. These were omitted. *14.* The points for 2,4-dinitrophenyl fluoride are concentrated at the lower end of the line. *15.* The point for pure benzene deviates to the left and has been omitted. Note that the activation energy *increases* as the alcohol content is increased. The deviation of the point for pure benzene suggests preferential solvation by the alcohol. Compare with scatter of the Menschutkin reaction in non-hydroxylic solvents. *16.* Energy of activation is higher in more polar solvents. The higher rate in more polar solvents at ordinary temperatures is due to the entropy. *17.* Only two of these points are brosylates. Neomenthyl tosylate was omitted. *18.* A group of chlorides, including those corresponding to the extremes of this series of iodides, have nearly constant E and log PZ. Since the bond to iodine is weaker, the transition state for iodides should be less like the ion pair (91). The iodides all have a more positive entropy than the corresponding chlorides. *19.* The hindered α-mesitylethyl chloride deviates to the right and was omitted. *20.* The more complex fructoside, sucrose, does not fit. *21.* Phenyl derivatives do not fall on the same line. *22.* The point for the one available *ortho*-substituted benzamide deviates more (to the left) from the *para* line in the acid-catalyzed series (reaction 34) than in the base-catalyzed series (reaction 35). There may be some doubt about the analytical method in these reactions, however. *23.* The fact that *ortho* substituents fall on a line with the others suggests a mechanism involving attack at neither the aromatic carbon atom nor the adjacent oxygen. Hammett (64, p. 123) has calculated b and its probable error for the relationship $\Delta S^{\pm} = a + b\Delta F^{\pm}$ and, since he found that the probable error in b was large, concluded that the variation in $\Delta S^{\pm}$ might well be random. The present correlation coefficient differs from Hammett's calculation in two ways: $\Delta H^{\pm}$ rather than $\Delta F^{\pm}$ is correlated and the data include all 23 points of reference 88 rather than the eight *meta* and *para* points of an earlier paper. *24.* The line for the more hindered thymyl ketones is parallel and displaced to the left of the line for the less hindered carvacryl ketones. Omitted from the analysis of reaction 38 is the point for the least hindered member of that series methyl thymyl ketone, which appears to lie on the line for the less hindered carvacryl ketones (reaction 37). *25.* Rate constants for the reaction were based on an assumed first-order dependence on the concentration of catalyzing acid. Since this was not strictly true, and since the points represent different acid concentrations, this relationship should be treated with reserve. The range in activation parameters is highly unusual; they appear to be based on single rate constants at 25 and 35°. *26.* Data for five substituted picolinic acids in *p*-dimethoxybenzene fall on the same line. Reference 33. *27.* The data for disubstituted malonic acids do not spread enough to establish a linear relationship. Malonic acid itself falls on neither line. *28.* The two lines for the hindered and less hindered series are nearly parallel, with the less hindered one having higher E for a given log PZ. Two dixanthylenes have been studied, but they fall close together and with a lower E than points on the other two lines corresponding to the same log PZ. *29.* These two lines for the decomposition of benzene diazonium chloride in two classes of solvent are parallel but not identical. The separation (in the energy dimension) is about 0.7 kcal. Note that *meta* and *para* alkyl substituents in water produce a variation in log PZ of less than 1.1 unit as compared to the solvent effect of about 5 units (Ref. 93). If the effect of *ortho*, *meta*, and *para* substituents of a variety of types is examined the over-all result is a scatter (Ref. 44). *30.* The fact that the points for the "catalyzed" reaction appear to fall on the same line (although in different regions) as the points for the uncatalyzed reaction, suggests an essential identity of mechanism for the two reactions. *31.* Two points for the ϵ isomer are available, but they do not fall on the line of the β isomer in aqueous-alcohol mixtures. The same is true for three points available for the α isomer, but these form a line of their own. The α, γ, and ϵ isomers, all in 76% alcohol, form a line which does not include the β isomer.

TABLE I—*concluded*

The β isomer is the only one lacking adjacent hydrogen and halogen in a *trans* configuration. It is likely that the β isomer reacts by a different mechanism. *32.* The difference between the lines for the *cis* and *trans* compounds suggests a difference in reaction mechanism. *33.* Because all of these stilbene data fall on a single line it is likely that they represent a single mechanism rather than a non-adiabatic mechanism for those with low entropies and an adiabatic mechanism for those with high entropies. The low entropies of activation for some members of the series might be due to solvent orientation in a polar transition state rather than a nonadiabatic mechanism involving a quantum mechanically forbidden transition. In the absence of evidence that the stilbenes respond differently to paramagnetic catalysts, the adiabatic mechanism seems the more probable. *34.* The fit is better with the omission of the data for structural variation. *35.* Also fits Hammett $\rho\sigma$ plot. *36.* Gives a markedly curved Hammett plot. The point for *p*-methoxy deviates so much more than the rest from the E *versus* $\Delta S^{\pm}$ line that it has been omitted from the calculation. Therefore it is very likely that that compound decomposes at least partly by a different, probably polar, mechanism like that of *p-methoxy-p′-nitrobenzoyl peroxide in polar solvents* (91a). *Ortho* substituted peroxides form a rough line of their own roughly parallel but displaced below that of the *meta, para* line by about 2.5 kcal. There are not enough points on the *ortho* line to decide whether the ortho-methoxy compound is also abnormal. *37.* Although the isokinetic temperature is in the middle of the experimental range in this case, it is likely to be a non-spurious relationship since the range in $\Delta H^{\pm}$ and $\Delta S^{\pm}$ is large compared to the probable errors of those quantities. The differences in $\Delta H^{\pm}$ probably reflect differences in heats of desolvation of the azo compound in the various solvents. The order of increasing $\Delta H^{\pm}$ is such as to make that interpretation plausible. *38.* The point for cyclobutyl is very far from the line. This may mean a special feature in the mechanism for the cyclobutyl compound, but a decision will have to await the outcome of further experiments. The determination of the activation parameters for the cyclobutyl compound was based on the assumption that the reaction is solvent independent: data from different solvents were combined in the computation. *39.* This line also includes benzyl alcohol-toluene mixtures up to 50% toluene. The point for 75% toluene (omitted) falls midway between this line and the parallel one for non-hydroxylic solvents. *40.* The non-hydroxylic solvent line is about 3.6 kcal lower than the hydroxylic solvent line. *41.* Item 75 is presented as an example of the linear relationship existing between heats and entropies of solution as either the solvent is changed or moderate changes are made in the structure of the solute. It is one of many reported in reference 56. Such relationships have been derived theoretically for solution models that take into account orientation effects as well as sorting effects (121, 105, 104). The solution relationships are important in rate theory because linear relationships between heats and entropies of activation in a series of solvents may be derived if it is assumed that the heats and entropies of solvation of the transition states, as well as those of the reagents, are linearly related (144). The variation in $\Delta H^{\pm}$ and $\Delta S^{\pm}$ produced by structural changes in the reagent rather than the solvent can be divided into a purely internal part and a part due to the changed interaction with the solvent. The latter part should show the linear relationship on the same basis as in the case of the variable solvent. Similar experimental results have been obtained for the solubilities of inorganic solutes (108, 7, 73, 133). The solubility parameters for sodium and potassium chlorides and for potassium bromide in aqueous methanol give a fairly linear relationship up to water concentrations of about 80%, then break sharply (87, 84). Heats and entropies of hydration are linear for various alcohols and for ethylamine, but separate lines are needed for compounds of other types (30, 29). *42.* The point for nitrobenzene was included in the calculation of r, but is largely responsible for the poor correlation. It is about 2 kcal. below the line. *43.* Inclusion of *m*- and *p*- electron-releasing substituents leads to scatter. When they are included the total range of ΔH is only from -0.4 to $+0.55$, while the range in ΔS^{0} is -19.2 to -14.7. Excluding benzoic acid itself the range in ΔH is from -0.05 to $+0.55$ while the entropy range is not affected. The effect of structural changes on the ionization constant of benzoic acid is thus largely an entropy effect or the over-all isokinetic relationship is one of zero slope.

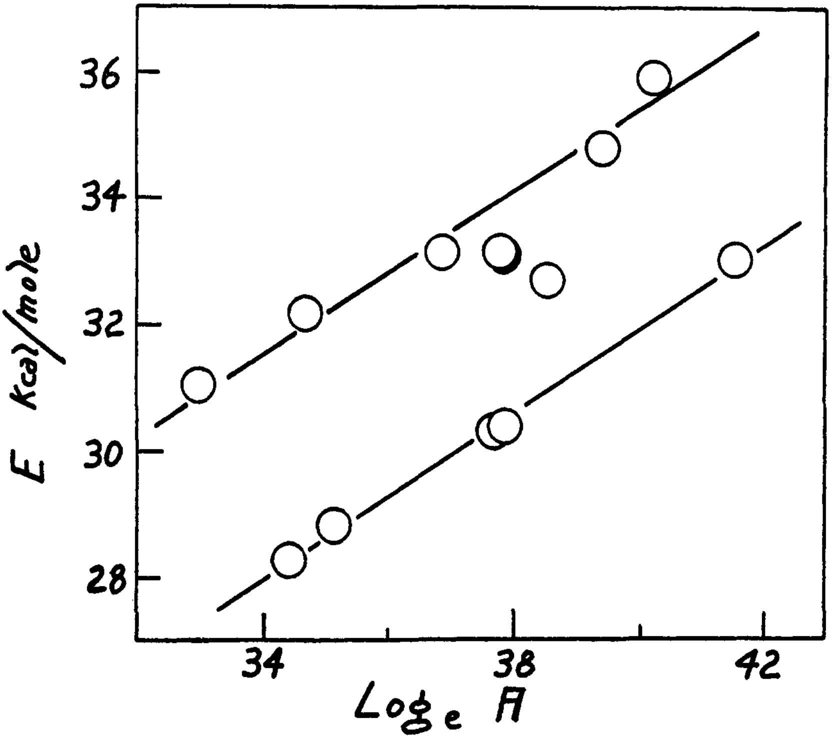


FIG. 4. DECOMPOSITION OF TRIETHYLSULFONIUM BROMIDE IN HYDROXYLIC SOLVENTS (upper line) AND NON-HYDROXYLIC SOLVENTS (lower line). The point nearly mid-way between the two lines is for a mixture of toluene and benzyl alcohol.

toluene fall on the line for hydroxylic solvents. The explanation for this discontinuous solvent effect may be similar to that advanced for the discontinuous effect of steric hindrance: either the ground or transition state has a double potential energy minimum. In some cases the correlation persists even when the structure and the solvent are both varied, while in others structural changes apparently alter the role of the solvent in the reaction. An example is found in Figure 5 in which the saponification of ethyl benzoate and ethyl *m*-nitrobenzoate in aqueous-organic media require separate lines. On the other hand the points for the saponification of valerolactone, phthalide, and 5-aminophthalide in alcohol-water mixtures are accommodated very nicely by a single line.

One source of the variation in both enthalpy and entropy of activation as the solvent is changed is the fact that the dielectric constant is a function of the temperature, important in reactions where dipoles or charges are generated or destroyed (64, page 84; 62b, page 15). As in the case of structural variation, it is expected that the purely electrostatic differences in solvents will lead to a linear relationship between the electrostatic part of the enthalpy and that part of the entropy. On the other hand there is completely convincing evidence that ionizing power is not entirely equivalent to dielectric constant but is a specific

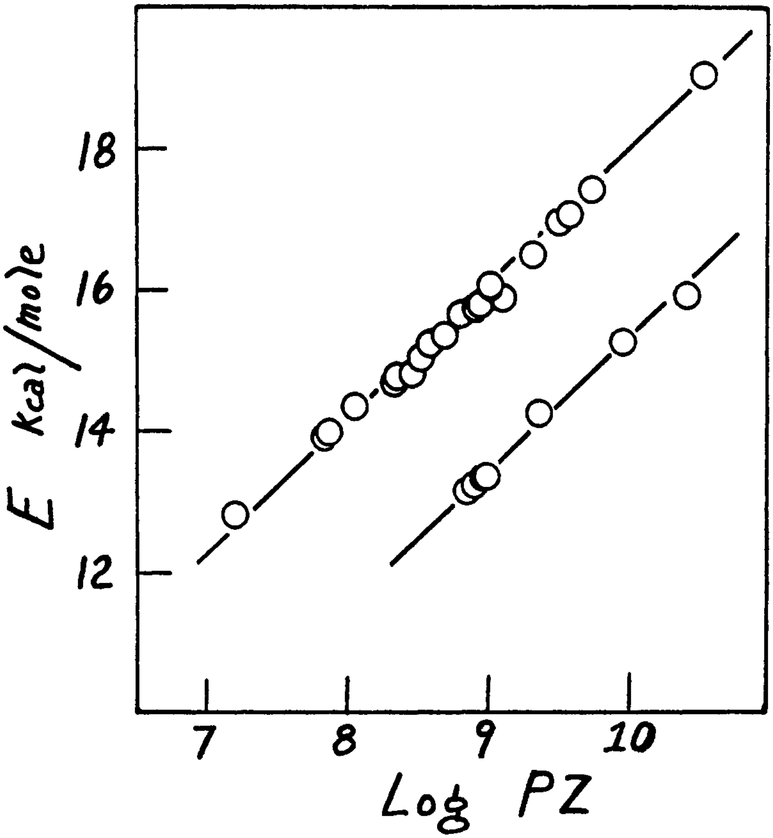


FIG. 5. THE SAPONIFICATION OF ETHYL BENZOATE IN AQUEOUS-ACETONE, AQUEOUS-ALCOHOL, ACETONE-ALCOHOL-WATER, AQUEOUS-DIOXANE (upper line). The saponification of ethyl *p*-nitrobenzoate in aqueous-acetone and aqueous-alcohol (lower line).

chemical effect. Thus the solvent ability of HCN for salts is not at all that to be expected from its high dielectric constant. Numerous polar reactions go at different rates in different solvent mixtures of equal dielectric constant. However, other solvation effects than those describable in terms of the dielectric constant can also be expected to contribute to the linear relationship. Statistical mechanical treatments indicate that the energies and entropies due to the mutual orientation of solute and solvent molecules will be linearly related (121, 105, 104). Finally, it is known empirically that heats and entropies of solution often are linearly related as well as heats and entropies of reaction.

Other theories predict the correlation on the basis of reaction rates determined by the quasi-crystalline vibrations of the solvent (36, 143) and the fact that the corresponding fluidity parameters are themselves correlated. Against the latter interpretation is the fact that correlations between reaction rate and fluidity seem to be limited to glasses or to nearly rigid solvents as demanded by the Rabinowitch-Wood theory (118).

Hydrogen bonding and similar specific solvent effects are probably of more importance than the dielectric constant or other macroscopic properties of the solvent. Thus we find that the predictions of the dielectric constant theory of medium effects, in the simplest form at least, sometimes fit and sometimes fail to fit the actual behavior of polar reactions. In considering solvent effects it is important to distinguish between the process of generating a charge on an object in a dielectric medium and the process of transferring an object already charged from a vacuum or medium of low dielectric constant to a medium of high dielectric constant (62b). It is the latter process that is pertinent here. A reaction that produces a polar transition state may be considered analogous to the process of charging a sphere. The following equations show the processes involved.

$$\begin{tikzcd}
 & \text{non-polar reagent} \atop \textit{in vacuo} \arrow[rr, "\Delta F_v^{\pm}"] & & \text{polar transition state} \atop \textit{in vacuo} \\
\text{Non-polar reagent} \atop \text{in polar solvent} \arrow[ur, "\Delta F_1"] \arrow[rr, "\Delta F_s^{\pm}"] & & \text{polar transition state} \atop \text{in polar solvent} \arrow[ur, "\Delta F_2"] &
\end{tikzcd}$$

It is clear from the diagram that $\Delta F_1 + \Delta F_v^{\pm} = \Delta F_s^{\pm} + \Delta F_2$. Assuming the absence of any but dielectric constant effects, ΔF_1 is equal to zero whence $\Delta F_s^{\pm} - \Delta F_v^{\pm} = -\Delta F_2$. The reduction in free energy of activation, and the changes in the other thermodynamic quantities of activation, would therefore be the same as the corresponding changes for the process of transferring the polar transition state from a vacuum to the polar solvent. For the common organic solvents the thermodynamic quantities for the latter process may be estimated from data on the dielectric constant and its temperature dependence (62b, page 19). The predictions on that basis are that the free energy, enthalpy, and entropy of activation are all lowered and that the change in free energy is largely due to the change in enthalpy.

Since the Menschutkin reaction between an amine and an alkyl halide develops a dipole, the prediction on a purely electrostatic basis is that the reaction will be faster in a more polar solvent, and largely because of a lower enthalpy of activation. Some Menschutkin reactions at least are in fact faster in more polar solvents at ordinary temperatures, as for example reaction number 18 of Table I. But, again referring to reaction 18, the purely electrostatic prediction of the effect on activation enthalpy and entropy is wrong. In this example rates are higher in more polar solvents not because of a lower enthalpy of activation but because of a less negative entropy of activation and in spite of an actual increase in enthalpy of activation. Thus the energy of activation is 6 kcal higher in ethanol than in benzene but the entropy of activation is 28 calories per mole per degree less negative in alcohol than in benzene (36a).

Possibly the difficulty comes not only from using the dielectric constant as a criterion of ionizing power but also from ignoring the solvation of the amine in the ground state. This will be greater in more polar solvents and some solvent will have to be removed from the amine in order to allow it to interact with the alkyl halide. If the liberated solvent is less constrained in the solvent structure than in the amine solvate both the higher energy of activation and less negative entropy of activation can be accounted for.

EVALUATION OF THE DATA

Table I contains all of the real or apparent isokinetic relationships known to the author up to the end of 1953. Some of the data are available as energies of activation (E) and logarithms of frequency factors (log PZ) while other data are available in the form of enthalpies of reaction or of activation ($\Delta H^{\pm}$) and entropies of reaction or of activation ($\Delta S^{\pm}$). A linear relationship between $\Delta H^{\pm}$ and $\Delta S^{\pm}$ implies a linear relationship between log PZ and E, and vice versa. In order to have a single basis for comparison, the slope, β, of only $\Delta H^{\pm}$ versus $\Delta S^{\pm}$ has been tabulated. It is readily calculated from the slope of the log PZ versus E relationship in cases in which the data are presented in that form. Again in order to have a single basis for comparison, the measure of precision tabulated is the correlation coefficient r, since r is independent of the units of the quantities correlated.

$$r = \frac{\overline{xy} - \bar{x}\bar{y}}{(\overline{x^2} - \bar{x}^2)^{\frac{1}{2}}(\overline{y^2} - \bar{y}^2)^{\frac{1}{2}}} \qquad \text{Equation 9}$$

In equation 9, x and y are the correlated variables and $\overline{x^2}$ is the mean value of x^2, etc. For the perfect correlation, $r = 1$.

Another column in Table I is the mid-point of the absolute temperature range within which the experiments were carried out. In evaluating the significance of the relationships it is necessary to compare the isokinetic temperature β with the experimental temperature before interpreting the value of r. It is possible to have an excellent correlation for a trivial mathematical reason. This may readily be seen by considering a hypothetical case in which all of the reaction rates at a single temperature are nearly the same. That might be because the temperature chosen happens to be the isokinetic temperature or it might be that the effect of the independent variable (structure or solvent) is actually negligible at *all* temperatures. Let us assume a case in which the latter is true. Then $\Delta F^{\pm} \cong$ a constant $= \Delta H^{\pm} - T_{\text{experimental}}\, \Delta S^{\pm}$ Equation 10. It is clear that $\Delta H^{\pm}$ as determined from the small, random variations in the rate constants will be a linear function of $\Delta S^{\pm}$ and that the slope, β, will be equal to the average of the experimental temperature range. Furthermore the correlation coefficient will necessarily be very close to 1. Those examples in Table I in which $\beta \cong T_{\text{exp.}}$ are therefore suspect, although there very likely are many cases in which the variation in $\Delta H^{\pm}$ and $\Delta S^{\pm}$ is real but β happens to fall in the experimental temperature range. Such cases are more likely to be significant when the data are accompanied by probable error figures for $\Delta H^{\pm}$ and $\Delta S^{\pm}$ and when the probable errors are small compared to the reported range of variation.

As might be expected, there is no sharp division between the possibly trivial cases discussed in the preceding paragraph and cases where β is different, but not very different, from $T_{\text{exp.}}$. The closer β is to $T_{\text{exp.}}$, the closer r should be to

TABLE II
REACTIONS OF INSUFFICIENT RANGE IN ENTHALPY OR IN ENTROPY OR INSUFFICIENT POINTS

Reaction	Ref.	Remarks
Saponification of saturated alkyl acetates in water.	100, p. 124	Constant E
Saponification of substituted benzyl acetates in 56% acetone.	139	Constant log PZ, nearly constant E.
Saponification of substituted phenyl acetates in 56% acetone.	139	Constant log PZ, nearly constant E.
Saponification of ethyl esters of aliphatic acids in 70% acetone.	132, 45	Nearly constant $\Delta S^{\pm}$
Saponification of *m*- and *p*-subst'd benzoic esters in 56% acetone.	139	Log PZ essentially constant except for *p*-NO_2;
	117	Trend, but $\Delta H^{\pm}$ range only 1 kcal.
Saponification of substituted benzoic esters in 85% alcohol.	78, 55	*p*-Compounds essentially alike except for NO_2, but *ortho*-nitro, chloro, and methyl are linear.
Saponification of *l*-menthyl benzoates in methanol.	137	Two tightly bunched groups of points, one for *o*- and one for *p*-substituents. The *p*-NO_2, *m*-NO_2, and *p*-CN fall outside of these groups and form a line.
Acid hydrolysis of aliphatic esters in 70% acetone.	45	Esters of normal acids have constant E and nearly constant log PZ. The ethyl esters of three hindered acids form a line.
	132	Series $\phi(CH_2)_{1\text{-}4}COOEt$ forms a line, but the range of E is only 0.5 kcal.
Acid hydrolysis of a series of benzyl and phenyl acetates in 56% acetone.	139	Forms two lines. Range of E only 0.5 kcal.
Electrophilic aromatic substitution.	100, p. 140; 80, 135, 62	Log PZ insufficiently variable.
Decomposition of *p*-substituted diazoacetophenones in acetic acid.	86	Range of $\Delta H^{\pm}$ is only 0.8 kcal.
Base-catalyzed bromination of acetone in aqueous acetic acid mixtures.	13	Roughly linear, but range of log PZ only 1.1.
Base-catalyzed bromination of acetophenone in aqueous acetic acid mixtures.	13	Linear, but range of log PZ only 1.4. Only three points.
Acid-catalyzed bromination of acetone in aqueous acetic acid mixtures.	13	Scatters, but range of E only 0.6 kcal, log PZ only 0.6.
Acid-catalyzed bromination of acetophenone in aqueous acetic acid mixtures.	13	Range of E only 0.7 kcal.
Iodination of acetone, various catalysts.	128	Nearly constant E, so in this case the Brønsted relationship is largely an entropy relationship.
Acid-catlyzed bromination of alkyl phenyl ketones in 75% acetic acid.	54	Rather small change in both E and log PZ. Linear for series $\phi\text{—}\overset{O}{C}(CH_2)_{1\text{-}4}CH_3$. Methyl (too little hindrance?) is below the line, and isopropyl (too much hindrance?) is above it.

TABLE II—*Continued*

Reaction	Ref.	Remarks
Isomerization of substituted benzene diazocyanides in benzene.	90	A linear trend with data that are only approximate. Range in E, 2.5 kcal; range in log PZ, 3.5.
Saponification of ethyl thiolacetate in three aqueous-acetone mixtures.	125	Apparent linear relationship. Range of E 13.0 to 14.4, range of log PZ 10.2 to 10.9.
H^+-cat. esterification of straight chain aliphatic acids with ethanol.	132	Essentially constant E.
H^+-cat. esterification of straight chain aliphatic acids with methanol.	57, 94, 130	Essentially constant E. Branched acids scatter.
Methyl iodide with *p*-alkyldimethylanilines in 10% acetone.	46	Essentially constant E and log PZ.
Methyl iodide with amines in nitrobenzene.	85	Two groups of essentially constant log PZ, *para*-substituted dimethylanilines and heterocyclic amines.
para-Alkyl and 2,4-dinitrobenzyl bromides with pyridine in dry acetone.	6	Essentially constant E and log PZ.
Para-substituted *ortho*-nitrophenyl bromides in piperidine as solvent.	10	Scatters, but range of log PZ is small.
Hydrolysis of *p*-alkylbenzhydryl chlorides in 80% acetone.	77	Good linear relationship of 4 points but only if the unsubstituted compound is left out. E from 18.9 to 20.1, log PZ from 11.1 to 11.6.
Solvolysis of diisopropyl phosphorochloridate in aqueous alcohol mixtures.	50	Rough correlation. E from 12.5 to 14.5, log PZ from 5.2 to 8.5.
Acid-catalyzed hydrolysis of peptides.	88	Rough correlation but $\Delta H^{\pm}$ varies only from 19.8 to 21.6. An enzymatic point is nowhere near the line.
Decomposition of di-*tert*-butyl peroxide.	120a	Almost independent of solvent in cumene, tri-*n*-butylamine, and *tert*-butylbenzene. Small, but significant difference in vapor phase. Small solvent effect may be due to steric hindrance to solvation.
Rate of mutarotation of glucose in water with different catalysts.	129	Roughly linear for water, acetic acid, chloroacetic acid, $HPO_4^{=}$ but not for H^+. Points for base catalysis scatter. Range in E, 1.6 kcal. Range in log PZ, 8. See reaction 63 of Table I for the behavior of the equilibrium constant.
Tetrafluorenylhydrazine dissociation equilibrium in five solvents.	36b	Range in ΔH^0, 1.2 kcal, is considered to be comparable to the probable error. Data group into essentially two points, one for heterocyclic solvents, the other for hydrocarbons. See reaction 69 of Table I.

TABLE II—*Concluded*

Reaction	Ref.	Remarks
Dissociation of hyrogen-bonded dimers of carboxylic acids in the gas phase and in benzene.	1	Range in ΔH^0 in the gase phase is about 12.4 to 15.2 kcal. ΔS^0 is nearly constant at about 33 to 36. This is about the entropy increase to be expected on converting one molecule into two molecules. Note that in solution in benzene the range of ΔS^0 is 20.6 to 27.8 (for the same standard state) while ΔH^0 varies from 7.8 to 9.4. There is a trend in the latter data. The difference in entropy between the gas phase and solution indicates considerable solvation of the acid monomer by benzene.
Oxidation of substituted azobenzenes with perbenzoic acid in benzene	4	Rough correlation, $\Delta H^{\pm}$ varies by about 3 kcal, $\Delta S^{\pm}$ by about 2.

1 before the correlation is convincing. The examples for which theoretical explanations should be sought are those in which a large difference between β and $T_{exp.}$ is coupled with a high degree of correlation or for which the range in $\Delta H^{\pm}$ and $\Delta S^{\pm}$ is large compared to the probable errors of these quantities.

Each rate constant defines a set of compatible combinations of $\Delta H^{\pm}$ and $\Delta S^{\pm}$ that could possibily produce that rate constant. Each such set of possible $\Delta H^{\pm}$ and $\Delta S^{\pm}$ values forms a straight line in the $\Delta H^{\pm}$, $\Delta S^{\pm}$ plane and the slope of each line is $T_{exp.}$. A set of rate constants thus produces a sheaf of parallel lines in the $\Delta H^{\pm}$, $\Delta S^{\pm}$ plane. The isokinetic line must intersect that bundle of lines. When β and $T_{exp.}$ are nearly the same, the isokinetic line and the bundle of lines intersect at an acute angle and every point on a line of the bundle is *necessarily* close to the isokinetic line. This is the reason for demanding not only a good r value when $T_{exp.}$ and β are not very far apart but also a significant range in $\Delta H^{\pm}$ and $\Delta S^{\pm}$ before concluding that the example in question is a genuine isokinetic relationship.

At or near the isokinetic temperature the range of $\Delta F^{\pm}$ values will be about the same as the range of scatter of the $\Delta H^{\pm}$ values about the isokinetic line. A qualitative statement of such an approximate isokinetic relationship is that the range in $\Delta F^{\pm}$ is very much less than it would be if the changes in $\Delta H^{\pm}$ and $\Delta S^{\pm}$ did not tend to counteract each other. Near the isokinetic temperature the small differences in rate are more the result of scatter of the activation parameters about the isokinetic line than they are the result of the difference between the temperature and the isokinetic temperature. Perhaps because they are largely the result of such scatter they rarely fall into any simple theoretical relationship such as the Hammett equation, while data whose spread is greater than that of the scatter about the isokinetic relationship usually do fall into some simple, explicable order.

TABLE III

REACTIONS OF APPARENTLY RANDOM VARIATION

Reaction	Variable	Ref.	ΔH or E	ΔS or $\log_{10}$ PZ
Menschutkin reaction in nitrobenzene with alkyl iodides.	Three alkyl iodides and five amines.	23, 25	E 9 to 17	log PZ 5.4 to 7.2
Menschutkin reaction in benzene.	Six alkyl halides and three amines.	149	E 8 to 18	log PZ 3.5 to 5.5
Menschutkin reaction of methyl iodide with pyridine in mixed non-hydroxylic solvents.	Composition of two-component solvents.	59	E 13.5 to 14.5	log PZ 4.5 to 7
Menschutkin reaction of methyl iodide with triethylamine, isopropyl iodide with pyridine, isopropyl iodide with triethylamine, methyl iodide with pyridine.	Composition of benzene-nitrobenzene mixture.	119	E 9.6 to 10.05 16.5 to 18.0 15.5 to 16.3 13.6 to 14.4 Gives mirror image-N-shaped curves as points are connected in order of increasing nitrobenzene concentration.	log PZ 4.3 to 5.8 5.3 to 6.7 3.9 to 5.7 5.3 to 7.0
Menschutkin reaction of ethyl bromide with triethylamine in acetone-benzene.	Acetone, benzene and three mixtures.	152	$\Delta H^{\pm}$ 11.7 to 12.2 (pure benzene is 11.19)	$\Delta S^{\pm}$ -40.3 to -42.4 (pure benzene -48.09)
Menschutkin reaction of methyl iodide with pyridine in non-polar solvents.	Solvent.	115	E 13.2 to 14.9	log PZ 4.3 to 7.6
Solvolysis of tosylates and brosylates in acetic acid.	Wide variation in structure.	150, 151	$\Delta H^{\pm}$ 22 to 31.5	$\Delta S^{\pm}$ -21 to $+8$
Solvolysis of alkyl chlorides in 80% alcohol.	Structure.	52, 22, 24	$\Delta H^{\pm}$ 18 to 30	$\Delta S^{\pm}$ -18 to 0
Solvolysis of cycloalkyl chlorides in 80% alcohol.	Ring size.	24	E 20 to 25	log PZ 14.9 to 16.3
Nucleophilic displacement by ions scatters in general. Only one case of a good correlation of more than three points is known. (Reaction 26, Table I) Example of scatter:	Most of the data concern variation of structure.			
RX + KI in acetone	R and X	52	$\Delta H^{\pm}$ 16 to 25	$\Delta S^{\pm}$ -24 to -6
Acid-catalyzed decomposition of azodicarbonate in aqueous dioxane.	Composition of the solvent.	83	E/RT at 25° 6.8 to 7.6	$\Delta S^{\pm}/2.3$ R 2.8 to 5.5

TABLE III—*Continued*

Reaction	Variable	Ref.	ΔH or E	ΔS or $\log_{10}$ PZ
Formation or neutralization of carbanions. Trends only.	Mostly structural.	61 (p. 131) 112, 97, 113	E 9 to 21	ΔS 6 to 15
Decomposition of trinitrobenzoic acid.	Solvent.	101	E 25 to 35	ln PZ 24 to 35
Diels-Adler reaction.	Rather large changes in structure.	70, 146	E 11 to 31	log PZ 4 to 12
Dehydrohalogenation of N-chloroaldimines by base.	Simultaneous changes in structure, solvent and base but only six points.	81	E 12 to 21	$\Delta S^{\pm}$ -44 to -2
Elimination of HCl in alcoholic alkali from para-substituted DDT's and DDD's.	Two types of structural change. The changes in E and in $\Delta S^{\pm}$ are nearly constant when a DDT is compared with the corresponding DDD.	41	E 18 to 23	$\Delta S^{\pm}$ -7 to 0
Decomposition of hydroxamic acids in 0.1 *N* ammonia	Structure of both parts of the molecule.	19	E 24 to 28. One point at 11	log PZ 14 to 18.5 One point at 6.7
Decomposition of O-ethyldithiocarbonate in dioxane - water mixtures gives an N-shaped plot.	Solvent dioxane-water.	35, 140, 141	E 17 to 21	$\Delta S^{\pm}$ 3.8 to 23.9
Gas phase dissociation equilibrium for trimethylboron-amine complexes.	Structure of the amine.	26, 21	ΔH^0 13 to 19	ΔS^0 39 to 45
Ionization of aliphatic acids in dioxane-water mixtures.	Solvent.	66	ΔH^0 -1.4 to 0	ΔS^0 -50 to -22
Ionization of benzoic acids with *meta* and *para* electron-releasing substituents.	Substituent.	18	ΔH^0 $-.05$ to $+.55$	ΔS^0 -19.2 to -17.2
Ionization of amines varying structure in water.	Wide structural variation.	17	ΔH^0 -6 to $+14$	$T\Delta S^0$ (at 25°) -5 to $+5$

The eighty-one examples of the isokinetic relationship in Table I have a mean r value of 0.979. In 20% of these examples β is within 20° of $\bar{T}$, the mid-point of the experimentally used range of temperatures. In 55% of the examples β exceeds $\bar{T}$ by 20° or more, while in only 27% of the examples does $\bar{T}$ exceed β by 20° or more. In 32% of the examples β exceeds $\bar{T}$ by at least 100°, while in only 9% of the cases does $\bar{T}$ exceed β by 100° or more. Thus β tends to be larger than $\bar{T}$. This means that for the majority of the reactions studied a change in solvent or structure that increases the activation energy decreases the rate at temperatures in the range used. Such reactions may be said to be governed by their enthalpies of activation in that temperature range. On the other hand in at least 27% of the examples studied the reverse is true, the rate definitely being governed by the entropy of activation. And in another 38% of the examples, an increase in temperature of 60° or less would put them in the entropy-controlled category.

It is a frequent observation that organic reactions are cleaner—*i.e.*, that the desired reaction is very much faster than competing reactions leading to isomers—at lower temperatures. A more general rule would be that a reaction is cleaner the further the experimental temperature is from the isokinetic temperature. At the isokinetic temperature the rates of formation of isomers (by the same mechanism) would be equal. Since $\beta - \bar{T}$ has more often been positive than negative, most reactions will be made cleaner by the use of lower temperatures.

Table II contains examples for which the data are inadequate in either number or range to test the existence of an isokinetic relationship. A number of trends are observable in these data, however. The enthalpy is approximately constant about as often as the entropy is.

Table III contains twenty-two examples in which the relationship between $\Delta H^{\pm}$ and $\Delta S^{\pm}$ appears to be random and the range appears to be beyond the limits of experimental error. Some of these examples involve rather drastic changes in structure, others are borderline cases that might well have been placed in Table II due to an insufficiently variable $\Delta H^{\pm}$ or $\Delta S^{\pm}$, still others are suspected of being partly inhomogeneous (51, 64a). The only conspicuous correlation of reaction type with a tendency to scatter is that about half of the examples in Table III either start with or produce ions. This is interesting in view of the prediction of the relationship by classical electrostatic theory for those reactions in which non-electrostatic interactions can be neglected (64).

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