JOURNAL OF **Pharmaceutical Sciences**

*August 1967* volume 56, number 8

*Review Article*

# Isergonic Relations and Their Significance for Catalysis

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CONTENTS



Received from the Department of Chemistry, University of Kansas, Lawrence, KA 66044

All errors of fact, judgment, and concept in this article are my own, but the same cannot be said for any truths which may be present. I wish especially to thank Professor E. E. Smissman for his encouragement and aid. Some of these ideas were presented in a lecture at the Fourth Annual Medicinal Chemistry Meeting-in-Miniature (MIKI Meeting) in Lawrence, Kan., last year, and I was greatly influenced by discussions with that group. Professor Bernard Belleau, who visited Lawrence in the Chemical Biology Seminar, and Dr. R. J. Thorn, whose visit was sponsored by the Chemical Physics Seminar, both contributed a number of insights. I would like to thank my colleagues and coworkers, especially Professors Earl S. Huyser and John A. *Landgrebe and Stephen* C. Hoops, H. Jayaraman, Larry Kershner, and C. G. Mitton, for many ideas and criticisms. I am grateful also for financial support by the National Science Foundation and National Institutes of Health of work discussed herein.

AN INTEREST in the phenomenon of catalysis, the acceleration of chemical reactions by substances having little or no effect on the gross stoichiometry, is shared by physical organic chemists and by medicinal chemists whose desire is to understand the character of enzyme action for purposes of drug design. The use of the concepts and theories of physical organic chemistry in the solution of problems of medicinal chemistry, such as the analysis of receptor sites and the synthesis of active compounds, is already well known to readers of the *Journal of Pharmaceutical Sciences*. In this article, the author would like to call attention to some current ideas in physical organic chemistry which are believed to have special relevance to the problems faced by pharmaceutical scientists, and to present some elementary applications of them to questions of catalysis.

**Transition-State Theory**—It is a nearly universal practice of solution kineticists today to present their results in terms of the transition-state theory (1–5), a custom justified by the enormous success enjoyed by this theory in producing a detailed understanding, in molecular language, of the mechanisms of a wide variety of organic and inorganic reactions. According to this theory, the reactants are viewed as participating in a quasi-equilibrium with the species (or configuration) at the maximum of energy separating the reactants from the next minimum of the Gibbs

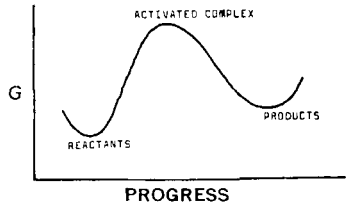



*Fig. 1—Free energy profile for a simple reaction.*

free energy surface[1] (Fig. 1). The maximum energy configuration (the *activated complex* or, colloquially, the *transition state*) is treated as a molecule for which "thermodynamic" functions (the free energy of activation, $\Delta G^*$, the enthalpy of activation, $\Delta H^*$, and the entropy of activation, $\Delta S^*$) may be defined using a quasi-equilibrium constant, $K^*$, for its formation from reactants[2] (Eqs. 1 and 2):

$$\Delta G^* = -RT \ln K^* \qquad \text{(Eq. 1)}$$

$$\Delta G^* = \Delta H^* - T\Delta S^* \qquad \text{(Eq. 2)}$$

The rate constant $k$ is then given by Eq. 3:

$$k = (\mathbf{k}T/h)K^* \qquad \text{(Eq. 3)}$$

where $\mathbf{k}$ is the Boltzmann constant, $h$ the Planck constant, and $T$ the absolute temperature. In addition to the free energy, enthalpy, and entropy of activation, other quasi-thermodynamic functions of activation may be defined and measured, notably the heat capacity and volume of activation, but these will not concern us here, although the volume of activation, in particular, may be of importance in catalytic processes (7).

The relevance of these considerations to problems of catalysis lies in the accuracy, economy, and elegance with which the activation parameters can be used to describe the molecular origins of reaction-rate variation with conditions (1–5, 7, 8). The understanding of the function of a catalyst must consist in the specification of the way in which it affects the activation parameters of the reaction of interest by interaction with the substrate and the activated complex.

Any mechanistic model, if formulated in sufficient detail, includes the relevant interactions. If the effect of each of these on the enthalpy and entropy of activation, and thus on the free energy of activation, is estimated, then the sum over all interactions gives the rate of the catalyzed reaction, relative to the rate of the uncatalyzed reaction or to the reaction catalyzed by another substance, *i.e.*, the *catalytic efficiency*. A similar estimation of the effect of changing the substrate structure on these quantities can yield the relative rates of the catalyzed reaction for various substrates, or the *catalytic specificity*.

The estimation process can be aided, and some general statements can be made, by use of relations which have been observed between the enthalpy and entropy changes associated with certain interactions, so that the two variables are not independent. In fact, it will be shown that the existence of such relations permits the formulation of a simple quantity which expresses numerically the catalytic specificity associated with a given kind of interaction in terms of its biological value.

Table I—Some Important Factors Which Contribute to the Enthalpy and Entropy Changes for Solution Reactions

| *Enthalpy:* Potential and Kinetic Energies; Work | *Entropy:* Statistical Probability |
|---|---|
| Covalent bonding | Number of particles (translational freedom) |
| Electrostatic attractions and repulsions, including those of dipoles | Freedom of external and internal rotations |
| Nonbonded attractions and repulsions (van der Waals and London forces) | Low-frequency vibrations |
| Hydrogen bonding | Freedom of translation and rotation of solvent molecules |
| Charge-transfer bonding | Symmetry |
| Strain and distortion of bond lengths and angles | |
| Solvation energies | |
| Resonance energies | |
| Zero-point energies | |
| Pressure-volume work | |

**Free Energy, Enthalpy, and Entropy**—For the convenience of the reader, Table I recalls the major factors contributing to the magnitudes of enthalpy and entropy changes for reactions in solution. From the standpoint of transition-state theory, it is immaterial whether these quantities refer to the conversion of reactants into products in an equilibrium process or to the conversion of reactants into activated complex in a rate process. No comment is really required about these factors, which are familiar to most people from discussions of reaction mechanisms. Wiberg (3) has discussed the subject in great detail in a very clear fashion. It should be mentioned that the form of the transition-state theory given here (unit transmission coefficient) is inapplicable to reactions involving changes in electron-spin multiplicity (9).

[1] This is the appropriate variable for the vertical axis of such plots (see the discussion in *Reference 6*). Johnston's objection (*Reference 5*, chap. 16) can be met by use of an appropriate standard state for the stoichiometric assembly for each set of experimental conditions. The step functions shown by Johnston are correct, rather than the curves shown here (and usually).

[2] $K^*$ is a quasi-equilibrium constant and the associated 'thermodynamic" functions are given quotation marks (or are designated quasi-thermodynamic) because the degree of freedom for decomposition of the activated complex has been removed from consideration. (See *Reference 4* for a recent, lucid discussion.)

## ISERGONIC RELATIONS

Should there exist a relation between the enthalpy change and the entropy change which occur during a chemical process? A number of models suggest that the answer is yes. Consider the formation of a bond between two polyatomic species. As the two particles combine, enthalpy (bond energy) is liberated and the translational and rotational entropy is decreased by the conversion of two particles into one. If a series of such association processes, of progressively stronger binding, were studied, the enthalpy liberated would increase with the stronger binding, but the translational entropy loss would be the same in all cases and the rotational entropy loss little different. However, stronger binding usually means shorter bonds, and for polyatomic species, the smaller separation of the more strongly bound moieties could easily lead to greater losses of entropy due to restriction of bending vibrations and internal rotations through mutual interaction. Thus stronger and more exothermic binding might well be accompanied by a progressively more negative entropy of combination.

Consider also the ionization of a neutral molecule in a solvent which interacts readily with ions. Suppose a series of dissociation rates is studied, such that the degree of conversion of the reactant into its ionic fragments at the activated complex steadily increases. As the ions become more fully formed, the solvent will interact more strongly with the activated complex with liberation of a correspondingly greater amount of solvation energy. At the same time, the tighter bonding of the solvent molecules will lead to an increasing reduction in entropy, as more solvent molecules become involved (translational and rotational entropy) and as the rotational and vibrational motions of those already bound are further restricted. Thus the solvation process should make increasingly more negative enthalpy and entropy contributions to the free energy of activation as the degree of charge separation at the activated complex increases.

Both of these models predict a *compensatory* relation of enthalpy and entropy, *i.e.*, a correspondence such that the effect of one quantity on the free energy tends to be cancelled by the effect of the other, but neither model (in the form above at least) is detailed enough to determine the functional form of the relation. For this we turn to experiment.

**Linear Compensatory Relations**—Alder and Leffler (10) observed that the enthalpies and entropies of activation for the decomposition of phenylazotriphenylmethane into free radicals in a series of solvents were related *linearly*, according to Eq. 4:

$$\delta_M \Delta H^* = \beta \delta_M \Delta S^* \qquad \text{(Eq. 4)}$$

with $\beta = 310°$ K.; the positive value of $\beta$ expresses the fact that the behavior is compensatory. The symbol $\delta_M$ occurring in Eq. 4 is the very useful Leffler-Grunwald operator (11) for medium variation. $\delta_M \Delta G^* = \Delta G_M^* - \Delta G_0^*$, where the subscript $M$ refers to some arbitrary solvent and the subscript 0 to a standard solvent. The expression $\delta_M \Delta G^*$ can conveniently be read, "the effect of medium on $\Delta G^*$." Other operators can be defined for any variable, such as structure ($\delta_R$), catalyst ($\delta_C$), *etc.* The net effect on the free energy of activation in the Alder-Leffler system is obtained by substitution of Eq. 4 into Eq. 2, after application of $\delta_M$ to the latter, yielding Eq. 5.

$$\delta_M \Delta G^* = (\beta - T)\delta_M \Delta S^* \qquad \text{(Eq. 5)}$$

This study illustrated that lack of a solvent effect on rate at a given temperature ($\delta_M \Delta G^* \sim 0$) could not be taken as evidence that no solvent-interaction change was arising on activation. In this case, at temperatures near 310° K., the solvation enthalpies and entropies cancel each other and no rate effect is found. The molecular interactions responsible for these observations for free radical reactions are still under investigation (12).

Since, in principle, no variation in rate at all would be observed if the reaction were studied at a temperature equal to $\beta$, this quantity was denoted the *isokinetic temperature* (13, 14). If enthalpy–entropy compensation is observed for an equilibrium process, this terminology is etymologically incorrect. Perhaps a more desirable general term is *isergonic temperature* (the slope of an *isergonic relation*, such as Eq. 4), which we adopt here.

Leffler and Grunwald (11) have collected a large number of isergonic relations for both rate and equilibrium processes, all approximately linear with positive slope, *i.e.*, compensatory in nature. The values of $\beta$ ranged from about 100° K. to about 1300° K.

The same authors have further shown that some data sets which did not yield isergonic reactions (in which enthalpy *versus* entropy plots either showed no correlation or a nonlinear one) could be analyzed in terms of a superposition of more than one isergonic relation (Eqs. 6–8):

$$\delta\Delta H = \sum_i \delta\Delta H_i; \ \delta\Delta S = \sum_i \delta\Delta S_i \qquad \text{(Eq. 6)}$$

$$\delta\Delta H_i = \beta_i \delta\Delta S_i \qquad \text{(Eq. 7)}$$

$$\delta\Delta H = \sum_i \beta_i \delta\Delta S_i \qquad \text{(Eq. 8)}$$

They reason that each of these terms in the summations corresponds to a particular interaction mechanism and that the observed enthalpies and entropies are merely the resultant. The plots may be analyzed by vector addition of the individual relations to obtain the locus of a given point. As shown in Eq. 7, each interaction mechanism is presumed to have its own characteristic isergonic temperature $\beta_i$. The reader will agree that such cases as this are likely to be of the greatest value in analyzing the most interesting cases of catalysis, in which manifold interactions between catalyst and substrate are expected.

**The Role of Experimental Error**—Two important criticisms of the use of isergonic relations have appeared. Petersen, Markgraf, and Ross (15) criticized most of the relations which had appeared before 1961 on the grounds that (*a*) the errors in $\Delta H$ and $\Delta S$ are related—if the temperature dependence of a rate or equilibrium constant is used to evaluate them, $\Delta H$ is obtained from the slope and $\Delta S$ from the intercept (effectively) of the same line—so that spurious relations may arise from experimental error, and (*b*) that a number of reactions showing apparent isergonic relations in fact had total ranges of variation of the enthalpy smaller than the maximum error in $\Delta H$, as estimated from the errors of the extreme temperature points of the Arrhenius or Eyring plots.

Leffler and Grunwald (11, 14) have shown, however, that this method of error analysis is incorrect, since if the maximum error of $\Delta H$ is placed on the enthalpy–entropy plot, it will include regions of impossibly high or low $\Delta G$ (in which the error is always much less than in $\Delta H$). The true error contour is thus an ellipse tilted with its major axis along a line of slope equal to the mean experimental temperature. It would appear that most of the originally described isergonic relations do in fact represent actual correspondences of enthalpy and entropy, although it emerges clearly from this controversy that larger temperature ranges than have been usual ought to be employed in the measurement of activation and thermodynamic parameters, inasmuch as the maximum error in $\Delta H$ increases as the inverse of the absolute temperature range studied.

Petersen (16) has raised a further objection to the use of isergonic reactions. If an isergonic temperature actually exists, he points out, then it is clear that the Arrhenius or Eyring plots for all the individual systems correlated must intersect at that point. No variation in rate at the isergonic temperature will then be observed. Petersen (*a*) constructed a set of artificial data which displayed a satisfactorily linear isergonic relation (correlation coefficient 0.998), but for which the individual Eyring plots did not intersect at a common point, and (*b*) found that in no case of an isergonic system from the literature did the Eyring plots have the requisite intersection property.

This demonstrates very convincingly that isergonic relations are approximate, a result which on reflection is more satisfying than the existence of exact relations. It would be amazing if the shift in enthalpy change produced by a structural or environmental variation were always accompanied by an exactly proportional entropy change; we are unaccustomed to such rigor in chemistry. On the other hand, the fact that structurally induced variations in $\Delta H$ and $\Delta S$ are in the same direction and approximately proportional is a very informative observation from a mechanistic point of view. Indeed, the isergonic temperature (or approximate change in $\Delta H$ per unit change in $\Delta S$) is directly useful inasmuch as it must be quantitatively consistent with an acceptable mechanistic model. Herein is the utility of the concept, rather than in the existence of an experimental temperature at which no rate variation is observed.

It is certainly true that Petersen's work shows the term isergonic temperature (or isokinetic temperature) to be a misnomer. Nevertheless, as Leffler has said (14), such a term is conveniently mnemonic as a name for the slopes of linear enthalpy–entropy relations.

**Solvation Phenomena and Electrostatic Interactions**—As we noted in the initial arguments above, an isergonic relation due to solvation effects might be expected for a series of reactants in an ionization rate process. The same arguments indicate that solvation energy and solvation entropy ought in general to be related in a compensatory way and that processes in which solvation changes contribute in a significant way to the energetics may exhibit the effects of this compensation.

In the case of solvation phenomena involving electrically charged species, however, we must consider the values of the enthalpy and entropy changes associated with the electrostatic work of separating the charges (in ionization) or the work done by their combination. The free energy change, enthalpy change, and entropy change [as obtained by Frost and Pearson (17) in a simple way] are given by Eqs. 9, 10, and 11:

$$\Delta G = (-Z_A Z_B e^2/Dr) \qquad \text{(Eq. 9)}$$

$$\Delta S = (-Z_A Z_B e^2/Dr)\,(\partial \ln D/\partial T)_P \qquad \text{(Eq. 10)}$$

$$\Delta H = (-Z_A Z_B e^2/Dr) \times (1 - T[\partial \ln D/\partial T]_P) \quad \text{(Eq. 11)}$$

where the $Z$'s are the charges (in units of the electronic charge) on the ions, $e$ the charge on the electron, $D$ the dielectric constant of the medium, and $r$ the charge separation in the initial state; the values are for separation of the ions to infinity. These and related expressions have been used and discussed critically by Frost and Pearson, by Lumry (7), and by Linderstrøm-Lang and Schellman (18) as well as many others. Their limitations are rather severe inasmuch as they ignore the difference between macroscopic and microscopic dielectric constant, treat the solvent as a continuum, and ignore particulate interactions of the solvent with the ions. As is evident from inspection, they do not predict any dependence on the structure of the ions; for example, $\Delta S$ of combination for univalent ions in water should be about $-10$ e.u. A number of cases do not depart seriously from this rule (17).

However, the heat and entropy of combination of all ions of the same charge type are not equal, as is implied by this treatment. Duncan and Kepert (19) collected the data of a number of workers on the thermodynamics of ion-pair formation for many different types of salts in several protic solvents. These data are correlated isergonically with a slope of 200° K. The explanation probably lies in the interaction of solvation energies and entropies in the hydration shells, as discussed above.

Brown (20), in a wide ranging study of isergonic relations, found that the data for ionization of a variety of organic acids were correlated by lines with an isergonic temperature of 280° K. This number is in striking agreement with an estimate by Belleau (21) of the isergonic temperature associated with the "melting" of the "icebergs" which, according to the Frank-Evans theory of the structure of aqueous solutions,[3] surround nonpolar solutes in water. The term "iceberg" being taken literally, the heat of fusion of ice (1440 cal./mole) was divided by the entropy of fusion of ice (5.6 e.u.) to obtain $\beta = 273°$ K. This agreement with Brown's finding supports an *ad hoc* hypothesis that these correlations are arising from formation and destruction of solvation shells surrounding the reactants and products, and that these shells bear some resemblance to ice.

Hepler,[4] in a landmark contribution to the understanding of chemistry in protic solvents, applied the isergonic temperature of 280° K. suggested by Brown's observations for solvation phenomena in water to the data for phenol ionization and arrived at a completely meaningful interpretation of the substituent effect on this reaction. This theory will be discussed in more detail under *Linear Free Energy Relations*, but at this point a particular property, noted by Hepler, conferred on solvation phenomena in water by the isergonic temperature of 280° K. should be brought to light. According to Eq. 5 above, the total contribution of solvation phenomena in any process to its free energy change is given by the change in solvation entropy times $(\beta - T)$; but since $\beta$ is very close to room temperature, the very important conclusion emerges from Hepler's theory that *solvation changes will have little effect on the rate or site of equilibrium of a reaction studied in aqueous solution near room temperature.*

**Linear Free Energy Relations**[5]—In his original discussion of the limitations of the Hammett equation (Eq. 12):

$$\log k/k_0 = \rho\sigma = \frac{\delta_R \Delta G^*}{-2.3\ RT} \quad \text{(Eq. 12)}$$

Hammett (24) noted that if the entropy change for a series of reactions were constant, then the free energy change would be equal to the enthalpy change, which might reasonably be expected to vary according to the potential energy changes which are usually considered to lie at the basis of such linear correlations. At a later time, Taft (25) showed this criterion to be too restrictive and demonstrated that linear free energy relations could result from data sets in which the entropy changes were not constant along the series but instead varied linearly (isergonically) with the enthalpy changes (Eqs. 4 and 13).

$$\delta_R \Delta G^* = \left(\frac{\beta - T}{\beta}\right) \delta_R \Delta H^* \quad \text{(Eq. 13)}$$

Studies of the ionization of substituted phenols in water by Hepler (23), already mentioned, produced data which were correlated by the Hammett equation but which fulfilled neither of the criteria just mentioned: the changes in entropy were far from constant (in fact, the major part of the substituent effect appeared in the entropy term) and they were not linearly related to the corresponding enthalpy changes. Hepler proposed to explain the data in a way which can be formulated as a two-interaction–mechanism isergonic relation. He assumed the enthalpy effects to be a sum of internal contributions ($\delta\Delta H_i$, essentially the potential energy effects customarily invoked for substituents) and external contributions due to solvation ($\delta\Delta H_e$) as expressed by Eq. 14:

[3] See Kavanau (22) for a summary of this and other ideas.
[4] See Hepler (23) and other papers by the same author.
[5] Readers unfamiliar with free energy relations should consult Wiberg (3) and then Leffler and Grunwald (8).

$$\delta\Delta H = \delta\Delta H_i + \delta\Delta H_e \quad \text{(Eq. 14)}$$

He assumed the observed entropies to comprise a similar sum but hypothesized the internal entropy changes (in the rigid aromatic system) to be negligible compared to those derived from solvation effects (an infinite isergonic temperature was thus assumed for internal changes since $\delta\Delta S_i = 0$). Thus, the observed $\delta_R\Delta S$ were taken equal to $\delta_R\Delta S_e$. Furthermore, on the basis of the observations of Brown cited above, he assumed the solvation energies and entropies to be isergonically related with an isergonic temperature of 280° K. (Eq. 15):

$$\delta_R\Delta H_e = (280)\delta_R\Delta S_e = (280)\delta_R\Delta S \quad \text{(Eq. 15)}$$

The observed enthalpies of ionization are then related to the corresponding entropies by Eq. 16:

$$\delta_R\Delta H = \delta_R\Delta H_i + (280)\delta_R\Delta S \quad \text{(Eq. 16)}$$

Notice that this relation could be represented graphically by an isergonic plot with $\beta_e = 280°$ with each experimental point displaced vertically (parallel to the $\delta\Delta H$ axis since $\beta_i = \infty$) from the line by an amount $\delta\Delta H_i$. Now if the substituent effect on the free energy is examined, Eq. 17 is obtained:

$$\delta_R\Delta G = \delta_R\Delta H_i + (280 - T)\delta_R\Delta S \quad \text{(Eq. 17)}$$

Since the experimental temperature for which the observed Hammett correlation of these data was made is near 280° (the data were for 298° as usual), the contribution of the entire solvation effect (contained in the last term of Eq. 17) is almost completely lost from the free energy. In fact, as Hepler points out, if the 280° isergonic temperature is generally applicable to solvation phenomena in water, then solvation effects are nearly always negligible and the Hammett equation "sees" only the potential energy contributions to the free energy. This explains why the Hammett equation in aqueous solution (or, as we shall see below, in other protic solvents) near room temperature is so much more successful than it "should be" in providing data explicable in simple potential energy terms.

It has been found (26) that Hepler's theory is not limited to aqueous solution, to ionization processes, or to equilibrium data. The enthalpies of activation and the entropies of activation for the methoxide-catalyzed methanolysis of aryl methyl carbonates in methanol (to give dimethyl carbonate and the phenol) appear to be unrelated. Rates of methoxyl exchange from tritium-labeled esters were found to be much slower than solvolysis so that addition to the carbonyl group of the ester by methoxide ion is the rate-determining step. The rate process under study then is essentially addition to an aryloxy-substituted carbonyl group. According to the Hepler theory, the vertical displacements of the individual points from an isergonic line for solvation interactions should give $\delta\Delta H_i$* for each substituent, the effect of the substituent on the internal enthalpy (roughly the internal potential energy) of activation. If 320° K. is adopted as the solvation isergonic temperature for methanol, these deviations in fact give an excellent correlation with the Hammett $\sigma$. The slope is consistent with inductive stabilization of the negative charge being introduced in the activated complex and with resonance stabilization of the electron density being released from the carbonyl group onto the aryl oxygen by addition of the methoxide ion. As predicted by the Hepler theory, the free energies are correlated (roughly) by the Hammett $\sigma$ and very well by the free energies of ionization of the phenols, determined under the same conditions.

Under the discussion of catalytic interactions, we shall see that Hepler's theory probably explains the great success of the Brønsted equation in correlating catalytic constants and basicities or acidities. It also seems entirely possible that the new and extremely successful applications of linear free energy relations to biological phenomena such as drug action, by Hansch (27) and others, will be found to rest in part on the existence of isergonic relations for certain perturbing interactions which cause their cancellation or near-cancellation from the observed free energy data.

Arnett and Burke (28) have recently shown as well that Hepler's theory explains the correlation they found between heats of ionization of acids in nonaqueous or water-poor media and free energies of ionization in water-rich media. They cite other data to support their opinion, which agrees with mine, that this theory underlies a "vast array of free-energy–structure correlations."

**Nonbonded Interactions**—This term is probably used most often to refer to the repulsive interactions between groups forced to exist closely enough to experience mutual repulsion of their outer electron clouds. No entropy change would be expected to result from this kind of interaction among structureless groups. However, if the groups contain a sufficient array of substructure that close steric interaction causes the restriction of internal rotations, or increases the frequency of vibrations (usually bends) which have a low enough initial frequency to have

some population of molecules in the excited vibrational states at ordinary temperature (and thus initially some vibrational entropy), then a reduction in entropy is expected to arise coincidentally with the onset of steric repulsion. If both of these processes came about concurrently and gradually, an enthalpy–entropy relation would be expected, with an increase in enthalpy (incursion of repulsion) being accompanied by a reduction in entropy (restriction of motions). This model thus predicts a negative isergonic temperature, which has not been observed for cases of this kind.

The reason perhaps lies in the very steep distance dependence of steric interactions: they arise only at very short distances and the associated energies then increase very rapidly as the distance is further shortened between the interacting groups (3). Furthermore, rotational motion can probably be restricted by mere development of a potential well within which the former rotor now sits stationary, but not experiencing any increase in potential energy; in fact the energy will have decreased due to the loss of the kinetic energy of the rotor. Thus as the two interacting groups approach, the internal rotations of the substructure probably are lost at distances too great for severe steric repulsion. Later, when the repulsion begins to increase the energy, the groups are already frozen and no further entropy can be lost.

The latter model is in agreement with some data collected and tabulated by Taft (25). The steric strain energies of activation for esterification and hydrolysis reactions of esters were (in effect) taken as equal to the deviations (in energy units) from the Taft equation plot of the experimental enthalpies. These are plotted *versus* the entropies of activation in Fig. 2. The model predicts effectively a sharp change from an isergonic temperature of zero (entropy loss with no accompanying energy change) to an isergonic temperature of infinity (energy increase with no further entropy change), which Fig. 2 shows to be the case.

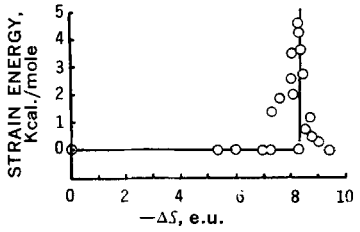



*Fig. 2—Strain energies of activation* versus *entropies of activation for hydrolysis and esterification of esters under various conditions, from the tabulation by Taft (25).*

**Charge–Transfer Interactions**—We have just seen that the restriction of internal rotations by steric interaction is unlikely to produce an observed relation due to contributions from the entropy loss of the former and the enthalpy increase of the latter; if some longer range force is simultaneously coming into operation, however, it might be possible to observe a relation between the enthalpy change from this source and the entropy loss from the restriction of internal rotations mentioned above. A possible system is offered by charge–transfer complexation of structured molecules.

A number of cases have been collected and examined for such correlations by Andrews and Keefer (29) An isergonic relation ($\beta$ = 690° K.) is found for the complexation in carbon tetrachloride solution of iodine and iodine monochloride with alkylbenzenes, *tert*-butyl alcohol, and dioxane (although most oxygen bases do not fit the same equation). A similar correlation is obtained for iodine with aliphatic amines in *n*-heptane solution ($\beta$ = 637° K.) and with nitriles, and for iodine, iodine monochloride, and iodine monobromide in carbon tetrachloride solution ($\beta$ = 540° K.). The absolute magnitudes of the entropy losses in the first cited series are from 3 to 9 e.u. The range (6 e.u.) is not inconsistent with the ascription of the variation to losses of internal rotations, for which values of 2–3 e.u. per rotation are probably appropriate.

The model fits the data in all respects, as noted by Andrews and Keefer. For example, the data for complexation of iodine with hexamethylbenzene ($\Delta H$ = −4 Kcal./mole, $\Delta S$ = −7 e.u.) and hexaethylbenzene ($\Delta H$ = −2 Kcal./mole, $\Delta S$ = −3 e.u.) indicate that the greater steric bulk of the ethyl groups restricts the complexing agent to a greater distance from the $\pi$-cloud, thus making the bonding less exothermic, but also requiring the restriction of fewer rotations, thus making the entropy change less negative. The values in general of $\beta$ about 600° appear to show that closer approach of the complexing agent, such that entropy equivalent to that of one internal rotation is lost ($-\Delta S \sim$ 2–3 e.u.), produces a bond about 1.2–1.8 Kcal./mole tighter than before.

**Hydrogen Bonding**—Hydrogen bonding is a long range force because the proton bridge, which *per se* has practically no steric requirement, serves to keep the two bonding moieties at a sufficient removal from one another that little or no steric interaction (an exceedingly short-range force) between the bonding groups is ex-

pected.[6] Thus, if a single hydrogen bond binds two species together, only the loss of translational entropy is expected, together with some entropy loss from restriction of rotation about the bonds forming the hydrogen bridge itself. Neither of these should vary much with the strength of the hydrogen bond, so that enthalpy–entropy relations would not be expected from this source. In aqueous solution, some changes in solvation on formation of the hydrogen bond might occur, leading to an isergonic relation with $\beta \sim 280$–$300°$, as discussed above.

The situation differs if more than one hydrogen bond forms between the same two bodies, or if the hydrogen bond is one of several forces binding the two moieties together. In this case the formation of the hydrogen bond should nearly always be accompanied by a loss of entropy, from restriction of internal rotational motions on conversion of linear into cyclic conformations and from conversion of low-frequency chain-deformation vibrational modes into higher frequency ring-deformation modes. Furthermore, ring formation of this type will promote closer steric interaction between the sides of the new ring, thereby restricting internal rotational motion to a still greater degree and probably increasing the frequency of some bending vibrations. In general, a stronger hydrogen bond, formed with greater liberation of enthalpy, ought to lead to a more rigidly restricted product and thus to a greater loss in entropy.

Although the data are not ideal for a test of this hypothesis, an isergonic plot has been constructed in Fig. 3 from a variety of measurements reported by Davies (31). The scatter is not surprising in view of the variety of types and sources of information included, but the correlation is satisfactory, with an isergonic temperature of about 270°. An entropy loss equivalent to freezing of one internal rotation (2–3 e.u.) thus results from strengthening of the hydrogen bonding system by about 0.5–0.8 Kcal./mole.

**Covalent Bonding**—Covalent bonding between structured species might be expected to generate isergonic relations in the same fashion described in the cases above for other types of bonding. Some of the many isergonic relations tabulated by Leffler and Grunwald (11) for association and displacement reactions may fall in this category, but the possibility of other origins remains open because of the universal complexity of the systems studied. Covalent bonds in organic compounds are generally formed with exothermicities of 30 to more than 100

[6] Covitz and Westheimer (30) have shown that such steric effects are not entirely negligible.

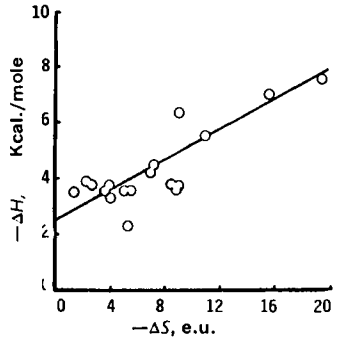



*Fig. 3—Compensation of energy and entropy in the formation for hydrogen bonds. The data are taken from Davies (31) and are for dimerization and polymerization in benzene solution of amides, measured by Davies and Thomas (32), and association of diphenylamine, phenol, and benzyl alcohol with dimethylformamide, dioxane, acetonitrile, benzyl acetate, and azobenzene in carbon tetrachloride solution, determined by Flett (33).*

Kcal./mole; if the formation is accompanied by the combination of two species into one, the entropy may decrease by as much as 50–60 e.u., while if the bond is formed intramolecularly, only 2–3 e.u. may be lost in the process. The simple ratios of $\Delta H/\Delta S$ thus range from 500 to 50,000° K., although this model cannot generate a continuously varying sequence of enthalpies and entropies.

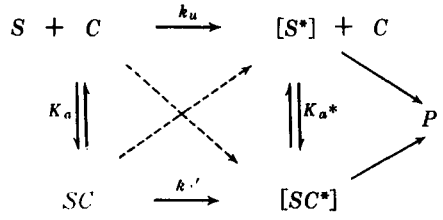
Thorn and his co-workers (34) have observed energy–entropy correlations in high temperature systems and have attributed the results to a fundamental relation between the energy of formation of a substance at the absolute zero and the entropy of the substance at higher temperatures, since structural information is present in both quantities. Thorn's efforts to develop the underlying theory promise to provide a complete statistical-mechanical basis for both isergonic and linear free-energy relations.

## QUESTIONS IN CATALYSIS

**A Simple Model of Catalysis**—To facilitate the consideration of catalytic processes, we will develop a simple model, based on the concept of virtual equilibria among activated complexes, recently applied by Kurz (35) to several mechanistic problems.

Scheme I portrays a system of reactions in which a substrate $S$ may be converted to a product $P$ by ($a$) a route catalyzed by $C$, involving formation of a substrate–catalyst complex $SC^*$, or ($b$) an uncatalyzed route through activated complex $S^*$. The rate law is given by Eq. 18:

$$v = k_c'[SC] + k_U[S] = [S](K_a k_c'[C] + k_U) \quad \text{(Eq. 18)}$$




*Scheme I*

It is readily shown that introduction of the extra, dashed routes makes no change. Scheme I also includes the equilibrium constant, $K_a^*$, for virtual interconversion of the activated complexes $S^*$ and $SC^*$, according to Eq. 19:

$$S^* + C \rightleftarrows SC^* \quad K_a^* \qquad \text{(Eq. 19)}$$

It does not matter that the actual interconversion does not occur directly; the concentrations of the two are the same as if it did. Then, since $k_c'K_a = k_UK_a^*$, the rate law may also be written as in Eq. 20:

$$V = [S](k_U + k_UK_a^*[C]) \qquad \text{(Eq. 20)}$$

This can be written in terms of the analytical concentration of $S$ ($[S]_{tot}$), for conditions of excess catalyst as Eq. 21, or in terms of the analytical concentration of $C$ ($[C]_{tot}$) for conditions of excess substrate (as in many enzyme experiments) as in Eq. 22:

$$V = k_U[S]_{tot}\left\{\frac{1 + K_a^*[C]}{1 + K_a[C]}\right\} \qquad \text{(Eq. 21)}$$

$$V = k_U[S]\left\{1 + \frac{K_a^*[C]_{tot}}{1 + K_a[S]}\right\} \qquad \text{(Eq. 22)}$$

The point is clear from either of these expressions that the larger $K_a^*$ is relative to $K_a$, the more efficient $C$ is as a catalyst. In other words, the stronger the association of catalyst with $S^*$ to form $SC^*$, the more rapidly the catalyzed reaction will proceed. Quasi-thermodynamic functions are of course associated with $K_a^*$ (Eq. 23):

$$\Delta G_a^* = -RT\ln K_a^* = \Delta H_a^* - T\Delta S_a^* \qquad \text{(Eq. 23)}$$

Let us divide up the free energy (and enthalpy and entropy) change on association of $S^*$ and $C$ into contributions from each of the interactions which occurs (Eq. 24):

$$\Delta G_a^* = \sum_i g_i = \sum_i h_i - T\sum_i s_i \qquad \text{(Eq. 24)}$$

Assume that $h_i$ and $s_i$ for each of these interactions are related, at least roughly, isergonically (Eq. 25):

$$h_i = \beta_i s_i \qquad \text{(Eq. 25)}$$

Then $\Delta G_a^*$ can be written as a sum in either enthalpies or entropies or both, for individual interactions (Eq. 26):

$$\Delta G_a^* = \sum_i (\beta_i - T)s_i = \sum_i (1 - T/\beta_i)h_i = \sum_j (\beta_j - T)s_j + \sum_k (1 - T/\beta_k)h_k \qquad \text{(Eq. 26)}$$

Notice that if the catalyzed reaction is to proceed faster than the uncatalyzed reaction, $\Delta G_a^*$ must be negative. Thus any interaction which contributes effectively to catalysis must have $g_i = (\beta_i - T)s_i < 0$. For interactions which involve binding of some kind, $s_i$ will usually be negative. Thus only if $\beta_i > T$ (the isergonic temperature exceeds the experimental temperature) is the interaction likely to enhance catalytic efficiency. Of the interactions considered in the last section, covalent bonding (probable $\beta \sim$ 500–50,000° K.) and charge-transfer bonding ($\beta \sim$ 500–700° K.) are clearly catalytic near room temperature, while hydrogen bonding ($\beta \sim$ 270° K.) and ion-pairing ($\beta \sim$ 200° K.) are noncatalytic.

Use of the average values for $\beta_i$'s obtained in the last section may give spurious results, however. All those values were obtained by use of systems where the forces were involved as primary (or very important) binding forces. In a catalytic activated complex, other forces may already hold a functional group in such a position that the interaction can occur with an abnormally small loss in entropy; the effective value of $\beta(\delta\Delta H/\delta\Delta S)$ will then be increased and the interaction becomes more catalytically effective. Thus, if a hydrogen bond with an enthalpic strength of 2 Kcal./mole were able to form with only a restriction of a single internal rotation (say, loss of 3 e.u.) in a preformed environment, $\beta_{eff} = 2000/3 \sim 700°$ K., and the interaction is nicely catalytic.

Conceivable interactions which come under scrutiny in the formulation of a mechanistic model can be designated (in the context of the activated-complex model) as *obligatory* (the model requires that they occur) or *elective* (the model makes no statement). Models will sometimes include obligatory interactions with positive $g_i$, *i.e.*, anticatalytic interactions. Steric repulsions which necessarily must be included to allow other, more favorable, interactions are examples. Of the elective interactions, those with $g_i > 0$ will not occur and may be omitted from the summation (that is, it is unreasonable to postulate that they occur). Those with $g_i < 0$ will occur and are catalytic. The best model is of course the one in which the obligatory and elec-

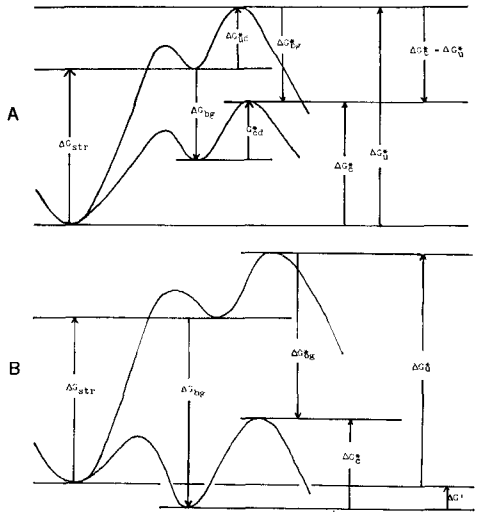



*Fig. 4—Key:* A, *distortion-catalysis in a system where the substrate is chiefly free;* B, *distortion-catalysis in a system where the substrate is chiefly complexed.*

tive interactions have been so balanced as to make $\Delta G_a^*$ as negative as possible.

Is the present model sufficiently sophisticated to apply to the complex kinetic systems frequently encountered in practice, particularly with enzymes? With some qualification, an affirmative answer is possible. Equation 22 is readily shown to be equivalent to the Michaelis-Menton equation. Lumry (7) has discussed in detail how experimental activation parameters from such a treatment can be related to mechanisms for more complex reactions. For our purposes, we need to regard $\Delta G_a^*$ as referring not to formation of a single activated complex $SC^*$ but rather an abstract weighted-average entity for all activated complexes along the reaction path. The weighting factor for the $i$th activated complex is exp $(G_i^*/RT)$.

**Catalysis by Strain and Distortion**—The view seems widely current[7] that many enzymes are catalytically active by virtue of the ability to induce in the substrate molecule some sort of strain or distortion, increasing its energy and thereby decreasing the energy required to transform it into a (presumably no longer strained) activated complex. Notable examples of such ideas are the "rack" hypothesis of Eyring and his co-workers (38) according to which the enzyme stretches bonds of the substrate, rendering their fission more facile; the proposal of Westheimer and his co-workers (39) that ribonuclease functions by intermediate formation of strained cyclic five-membered phosphate esters which, demonstrably in model systems, hydrolyze enormously more rapidly than their open-chain analogs; and the proposal of Bruice and Pandit (40) that esterases may bind esters in the unfavorable *trans* rotameric form, facilitating attack at the carbonyl group by nucleophilic reagents.

These hypotheses must be considered in two different ways, depending upon whether the major form of the reactant in limiting concentration under the conditions of interest is the free substance or the substance bound in the enzyme–substrate complex. Both circumstances are shown in Fig. 4. Figure 4A, refers to the former situation (free reactants). We compare the catalyzed reaction (lower curve) with the (perhaps hypothetical) uncatalyzed reaction passing through the strained or distorted form (pictured as the high minimum) along the upper curve. Shown on the diagram are $\Delta G_{str}$, the increase in free energy of the substrate on conversion to the strained form; $\Delta G_{bg}$, the free energy released on binding of the strained form of the substrate to the catalyst; $\Delta G_{ud}^*$, the free energy of activation for conversion of the strained substrate to the uncatalyzed activated complex; $\Delta G_{cd}^*$, the similar quantity for conversion of the strained-substrate–catalyst complex to the catalyzed activated complex; $\Delta G_U$, the over-all free energy of activation for the uncatalyzed reaction; and $\Delta G_C$, the over-all free energy of activation for the catalyzed reaction. It is graphically obvious that the entire catalytic efficiency, $\Delta G_U - \Delta G_C$, is given by the free energy of binding of the catalyst to the activated complex, the distortion energy cancelling out of the observable quantities. Thus the distortion, while surely an interesting characteristic of the catalytic mechanism, does not directly enter into the catalytic efficiency. This model applies to enzymatic catalysis at such reactant concentrations that the velocity is considerably less than maximum.

Figure 4B, shows the other possibility, the same quantities being displayed on the diagram. Here the complex is more stable than the free reactants. Inspection now shows that the catalytic efficiency is given by $-\Delta G_{bg} + \Delta G'$, where $\Delta G'$ is the excess of binding free energy over strain free energy for the complex (expressed as a positive number). The larger $\Delta G'$, the less effective the catalysis; the more negative $\Delta G_{bg}$, the more effective the catalysis. Once again, the important point is that the catalyst bind strongly to the activated complex relative to the reactant.

Thus the methods of reasoning given above apply to these cases equally well.

[7] For a discussion of this and the enthalpy–entropy question in intramolecular catalysis, omitted here for lack of space, see *References 36* and *37*.

TABLE II—ACTIVATION PARAMETERS FOR THE MUTAROTATION OF GLUCOSE ANALYZED BY HEPLER'S ISERGONIC THEORY[a]

| Catalyst | $\Delta H^*$)[b] | $\Delta S^*$)[c] | $\delta_C \Delta H^*$)[d] | $\delta_C \Delta S^*$)[d] | $\delta_C \Delta H$ | $\delta_C \Delta H_i$ |
|---|---|---|---|---|---|---|
| $H_2O$ | 17.2 | −24.9 | (0) | (0) | (0) | (0) |
| $HCO_2^-$ | 17.1 | −15.2 | −0.1 | +9.7 | +2.7 | −2.8 |
| $CH_3CO_2^-$ | 18.2 | −10.4 | +1.0 | +14.5 | +4.1 | −3.1 |
| $NH_3$ | 13.3 | −17.6 | −3.9 | +7.3 | +2.0 | −5.9 |
| Glucosate ion | 17.3 | −0.4 | +0.1 | +24.5 | +6.9 | −6.8 |
| $HO^-$ | 18.3 | +11.8 | +1.1 | +36.7 | +10.0 | −8.9 |

[a] Data are from Schmid, H., and Bauer, G., *Monatsh Chem.*, **96**, 1503(1965) All enthalpy data are in Kcal./mole; entropies in e.u. [b] Errors are about ±0.4 Kcal./mole. [c] Errors are about ±1.5 e.u. All figures are given, even if not significant.

**Acid–Base Catalysis and Catalytic Efficiency**—Catalytic efficiencies for acid-base catalysis are most frequently described by the Brønsted relation (Eq. 27), one of the oldest linear free energy relations (41–43):

$$\delta_C \Delta G^* = \alpha \delta_C \Delta G^\circ \qquad \text{(Eq. 27)}$$

Here $\Delta G^*$ is the free energy of activation, $\Delta G^\circ$ the free energy of neutralization or ionization of the catalyst, and $\delta_C$ the Leffler-Grunwald operator for catalyst variation. It was early rationalized (41) in terms of intersecting Morse curves, implying that potential energy variations were at its basis, while Leffler (44) later provided a noncommittal free-energy argument. In any case, examination of activation parameters for various catalysts correlated by the equation frequently reveals startling irregularities (45). Exemplary are the data of Schmid and Bauer (46) for the mutarotation of glucose, shown in Table II.

The validity of the Brønsted relation under these circumstances is understandable in terms of Hepler's isergonic theory, outlined above. Following Hepler, we assume $\delta_C \Delta S^* = \delta_C \Delta S_e$, entirely due to solvation. Furthermore, we assume $\delta_C \Delta H_e = 280 \delta_C \Delta S_e$ and that $\delta_C \Delta H^* = \delta_C \Delta H_i + \delta_C \Delta H_e$. These quantities are all listed in Table II. Note that the $\delta_C \Delta H_i$ are all negative and decrease with increasing basicity of the catalyst. These quantities are the enthalpies for the process shown in Scheme II.

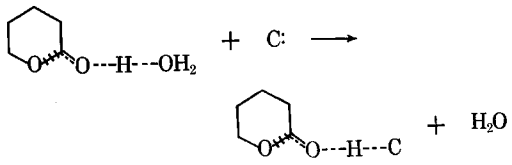
They are therefore effectively the strengths of the hydrogen bonds by which each catalyst is bound to the activated complex. The values are unreasonably large for ordinary hydrogen bonds, in agreement with a recent suggestion that unusually strong hydrogen-bonding capabilities are displayed by polarizable activated complexes.[8]

The Brønsted relation holds because, as shown in Eq. 28,

$$\delta_C \Delta G^* = \delta_C \Delta H_i + (\beta - T)\delta_C \Delta S \approx \delta_C \Delta H_i \qquad \text{(Eq. 28)}$$

$\delta_C \Delta G^* \approx \delta_C \Delta H_i$, because $\beta = 280^\circ \approx 298^\circ$

[8] See *Reference 47*. For another point of view, see *References 48* and *49*.




*Scheme II*

Furthermore, this makes the Morse curve argument and the Leffler rationale essentially equivalent.

**The Hydrophobic Bond**—Many discussions of this phenomenon have emphasized the "entropic" driving force of the liberated water molecules in stabilizing the combined form of nonpolar solutes or side chains in water, while others (7) have postulated an increase in the strength of hydrogen bonding by these liberated molecules.

If the solvation changes involved here are also described by Hepler's isergonic theory, then we can write for the free energy of combination of two nonpolar solutes:

$$\Delta G = \Delta G_i + \Delta H_e - T\Delta S_e = \Delta G_i + (\beta - T)\Delta S_e \qquad \text{(Eq. 29)}$$

and regardless of which effect is postulated above, $\beta \approx 280^\circ \approx T$ and $\Delta G \approx \Delta G_i$. This suggests that the actual driving forces are simply dispersion forces, *etc.* Of course the driving force may experimentally *appear* to be entropic if $\Delta G_i \approx -\Delta H_e$ by coincidence.

**Catalytic Specificity and Free Energy**—By a simple extension of the above model for catalysis we can examine the relative rates of reaction of two different substrates (catalytic specificity) by using the virtual equilibrium constant of Eq. 30 and its associated functions (Eqs. 31 and 32):

$$S_1 + S_2C^* \rightleftarrows S_2 + S_1C^* \; K_{12}^* \qquad \text{(Eq. 30)}$$

$$\Delta G_{12}^* = -RT \ln K_{12}^* = \sum_i g_i \qquad \text{(Eq. 31)}$$

$$g_i = h_i - Ts_i = (\beta_i - T)s_i \qquad \text{(Eq. 32)}$$

which, as before, are divided into contributions from individual interactions. $g_i$ is then the change in free energy of the $i$th interaction of the

catalyst on interchange of $S_2$ for $S_1$ at the binding site. A negative value of $\Delta G_{12}^*$ means a faster reaction for $S_1$; a negative value of $g_i$ means that the $i$th interaction favors a faster reaction with $S_1$.

A large negative value of $\Delta G_{12}^*$ means that the reaction is much faster for $S_1$ than for $S_2$ and the catalyst is said to be "specific" for $S_1$.

Assume the catalyst is reasonably specific for $S_1$. The interactions which confer this specificity are likely to be binding interactions for which the $s_i$ (Eq. 32) is negative. In order for the interaction actually to contribute to specificity, $(\beta_i - T)$ must also then be positive; the more positive it is, the more effective the interaction in aiding the catalyst to discriminate between $S_1$ and $S_2$, for a given amount of binding.

Just as was found with efficiency, above, a large value of $\beta_i$ permits an interaction to contribute strongly to catalytic specificity. The phenomena of specificity and efficiency, as Lumry (7) predicted, would appear strongly linked.

**The Biological Value of Specificity: Information and Entropy (50–54)**—The present treatment permits an interesting look at catalytic specificity in a living system in terms of its value to the system. Why are biological catalysts generally unusually capable of selecting one substrate over another? The probable answer is that any other course would lead to chaos in the cell—to a general breakdown of the intricate metabolic scheme which underlies continued life. This intricate metabolic scheme is a pattern of information and the value of enzymatic specificity is that it preserves this information.

Many authors have discussed the relation of information to entropy and the fact that living systems, because of their high information content, are reservoirs of negative entropy. As was seen above, the interactions which lend specificity to catalysts are likely to be ones of negative entropy—in order to "see" that it has the right substrate, the enzyme must bind it intimately (the *total* entropy of binding or catalysis may, of course, have any sign or magnitude).

Consider the free energy change when a "wrong" substrate is bound in preference to a "right" one (in Eq. 30 let $S_1$ now be "wrong" and $S_2$ "right"); $\Delta G_{12}^*$ must be positive (in order for the "wrong" reaction to be slower). For specificity-conferring interactions, as was just argued, $s_i$ will be positive. The more "wrong" the substrate is, the more positive $s_i$ will be. This is reasonable since if the "wrong" reaction occurs, information will be lost to the system (and its entropy will increase). In fact, if one bit (binary unit) of information (the amount required to answer one yes-or-no question) is lost, the associated increase in entropy is $R \ln 2$, or 1.4 e.u.[9] By what factor will the rate decrease if this much information is to be lost? The answer is given by $g_i$: for each increment of 2.3 $RT$ (1.42 Kcal./mole of 37° C.), the rate will decrease by a factor of 10. The ratio $g_i/s_i$ for any interaction then gives the ratio of decrease in rate of the specific reaction ($x$ powers of 10) which will occur if the structure of the substrate is sufficiently "wrong" that $y$ bits of information are lost (Eq. 33):

$$\frac{g_i}{s_i} = \frac{(2.3\ RT)x}{(R \ln 2)y} \cong 1000\ \frac{x}{y} = (\beta_i - T) \quad \text{(Eq. 33)}$$

This is just $\beta_i - T$ for the interaction in question. In fact $x/y$ (in units of orders/bit) $= (\beta_i - T)/1000$ can be called the *informational specificity* of an interaction. For reasonable ranges of $\beta_i$, estimated above, these are listed for a few interactions in Table III.

TABLE III—INFORMATIONAL SPECIFICITY AT 37° C. FOR SOME CATALYTIC INTERACTIONS

| Interaction | $[(\beta_i - T)/1000]$ orders/bit |
|---|---|
| Covalent bonding | 0.2 to 50 |
| Hydrogen bonding | 0 to 2.2 |
| Electrostatic bonding | 0 to 1 |
| Charge-transfer bonding | 0.5 to 0.8 |

Modification of the model should be possible to include specificity hypotheses such as "wrong-way binding" (56).

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[9] For an introduction, see *Reference 55*.

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## Research Articles

# Simultaneous Determination of Dissolution and Partitioning Rates *In Vitro*

By P. J. NIEBERGALL, M. Y. PATIL, and E. T. SUGITA

**An *in vitro* method is presented for the simultaneous determination of the dissolution and partitioning rates of drugs. The kinetics of the system is described, and a number of methods are given for evaluating the rate constants. The effects of stirring rate and temperature upon the rate constants were investigated and found to be in agreement with what would be expected for diffusion-controlled processes.**

THE DISSOLUTION rate of a drug may have a marked effect upon the absorption of the drug from a solid dosage form. This has led to an increasing interest in developing *in vitro* dissolution rate tests that can be correlated with *in vivo* absorption rate studies for possible use in quality control or for use in setting official standards. In addition, dissolution rates have been used to evaluate formulation variables under the assumption that all other things being equal, the drug formulation that dissolves most rapidly would have the greatest chance of clinical success.

The over-all absorption process for solid drugs, however, consists of the dissolution step followed by drug partitioning into an essentially lipid barrier. The three phase "rocking apparatus," developed by Doluisio and Swintosky (1), appears to have great promise in studying the effects of additives or of molecular modification upon the partitioning rates of drugs. This apparatus, however, cannot be used to investigate the dissolution process, and therefore is useful only for drugs in solution. Thus, the over-all process of absorption

Received February 20, 1967, from the Department of Pharmacy, The Philadelphia College of Pharmacy and Science, Philadelphia, PA 19104
Accepted for publication May 5, 1967.