Letter to the Editor

Iceberg Formation and the Resulting Effects on Rates of Hydrolysis of Aspirin

Several further points should be made in the debate regarding postulated iceberg formation and the resulting effects on rates of hydrolysis of aspirin (1). While changes in solvation are likely to be involved in the transition states for reactions in aqueous solutions at various temperatures, I am in general agreement with the criticisms of this paper (1) made recently by Anderson and Darrington (2), especially with regard to the interpretation of linear enthalpy-entropy relationships. These relationships are usually employed to examine either (i) a single solute in a variety of solvents or (ii) a group of solutes undergoing the same mechanistic process in one solvent. The use of linear enthalpy–entropy plots to postulate the involvement of a compensatory solvation process must be supported by a corresponding linear enthalpy-free energy plot (3) to obviate the effects of correlated error.

It is commonly assumed in reaction kinetics, as long as the reaction mechanism does not change, that the Arrhenius equation (or the more thermodynamically based Eyring equation) is obeyed over a temperature range. The basis of this assumption is that the preexponential factor, A, and the energy of activation, E_a (or the changes in enthalpy, $\Delta H‡$, and entropy, $\Delta S‡$, of activation for the Eyring equation) are independent of temperature. Although the temperature dependences of these quantities are not usually evident over narrow (10–20°C) temperature ranges, they are when the temperature range is as wide as in the debated study (1). Kishore and Nagwekar (1) have taken the position that each discrete change in slope in their Arrhenius plots represents a change in reaction mechanism, such that the arrangement of water molecules involved in the transition state differs for each temperature range. The activation parameters for any reaction are related to absolute temperature, T, by the heat capacity change at constant pressure, $\Delta C_p^‡$, according to the following thermodynamic identity:

$$\Delta C_p^‡ = \left(\frac{\partial \Delta H‡}{\partial T}\right)_p = T\left(\frac{\partial \Delta S‡}{\partial T}\right)_p = -T\left(\frac{\partial^2 \Delta G‡}{\partial T^2}\right)_p \quad (1)$$

where the subscript p refers to constant pressure and $\Delta G‡$ is the free energy of activation (4). This identity combined with the Gibbs-Helmholtz equation ($\Delta G = \Delta H - T\Delta S$) leads to

$$\Delta G‡ = \Delta H_o^‡ + \int \Delta C_p^‡ \, dT - T\int \frac{\Delta C_p^‡}{T} dT - T\Delta S_o^‡ \quad (2)$$

which may be integrated, Eq. (3):

$$\Delta G‡ = \Delta H_o^‡ + T\Delta C_p^‡ - T\ln T\Delta C_p^‡ - T\Delta S_o^‡ \quad (3)$$

In Eqs. (2) and (3), $\Delta H_o^‡$ and $\Delta S_o^‡$ are integration constants which could be regarded as the changes in enthalpy and entropy of activation for the reaction at absolute zero. Combination of Eq. (3) with the van't Hoff reaction isotherm, Eq. (4), leads to Eq. (5), known as the Valentiner equation:

$$\Delta G‡ = -RT\ln K‡ = -RT\ln k\frac{Nh}{RT} \quad (4)$$

$$-\log K‡ = \frac{\Delta C_p^‡ - \Delta S_o^‡}{R\ln 10} + \frac{\Delta H_o^‡}{RT\ln 10} - \frac{\Delta C_p^‡}{R}\log T \quad (5)$$

where $K‡$ is the equilibrium constant for formation of the transition state, k is the reaction rate constant, N is Avogadro's number, and h is Planck's constant. This exact thermodynamic treatment has been described for the temperature dependence of equilibrium processes (5) and has also been applied to reaction rate constants (6).

Equation (5) indicates that for $\Delta C_p^‡ \neq 0$, plots of log k vs $1/T$ must be nonlinear. Further, there is no single value for either $\Delta H‡$ or $\Delta S‡$, but values may be calculated at any temperature of interest. Hence, plots with changes in slope such as Fig. 1 in the paper of Kishore and Nagwekar (1) are expected. However, such a plot should be interpreted in terms of the thermodynamic treatment described above. Among other benefits, this treatment should allow extrapolation to low-temperature shelf lives with greater accuracy than the Arrhenius equation. Significant deviations from Eq. (5) may then be examined for more obscure causes. Discontinuities should be regarded with suspicion until confirmed unequivocally. It would have been of great value to obtain rate constants in the critical regions of Figs. 1 and 2 where discontinuities are apparent (55–60°C).

A flaw in the statistical treatment used to distinguish the slopes of the three subsets of data (1,7) is the assignment of a separate degree of freedom to each experimental point on the plots. The proper procedure is to average the replicated rate constants for each value of $1/T$ and then to assign one degree of freedom for each value of the independent variable. The replicates verify the precision of the experimental method used for the determination of rate constants but contain no additional information about the model to which the data are to be fitted. When the data (1) are fitted to the Arrhenius equation (requiring 2 degrees of freedom), each subset (30–40, 45–55, and 60–70°C) now has only 3 or 4 degrees of freedom remaining for hypothesis testing with Student's t, and the critical t values at $P < 0.01$ (7) are much greater. This invalidates the second of the two examples used to illustrate (7) the statistical test used and considerably weakens the first.

Richard J. Prankerd
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Editorial

The year 1992 marks an important turning point in the development of *Pharmaceutical Research*. Subscription to the journal has become optional, thereby granting AAPS members the freedom of choice among a growing list of publications. According to the long range plan of the AAPS, adoption of more Section journals will afford new opportunities to the AAPS, but it also poses challenges for *Pharm. Res.* as the flagship journal with the mission to provide a common forum for each Section and the AAPS as a whole. The Editorial board of *Pharm. Res.* will meet the challenge by a renewed emphasis on scientific excellence, striving for the journal of highest quality that can be attained in the pharmaceutical sciences. *Pharmaceutical Research* will continue to cover all areas of the pharmaceutical sciences, irrespective of the adoption of Section journals intended to meet special publication needs that cannot be accommodated in a more general journal.

With this issue we have implemented a new policy on the classification of manuscripts. All original research papers submitted to *Pharm. Res.* are either classified as a Technical Note or a Report, whereas subsequent classification as a full Research Article requires the explicit recommendations of referees and editors. Reports exceeding the recommended page limit must receive above average evaluations, but it is the prerogative of the editors to decide on the acceptability of a paper, with due consideration of the need to document all essential experimental details. Classification as a Research Article will be restricted to 10% of all papers published at the most, as a special recognition of extensive and important work. Such editorial judgments are subjective, and it will take time until the selection process is optimized and the requisite quality of Research Articles generally appreciated.

On behalf of the AAPS, I take this opportunity to acknowledge the tremendous contributions of each of the Associate Editors and the Editor for Europe. Their commitment and time-consuming efforts are essential to the success of the journal, and it speaks for the stature of AAPS that such outstanding individuals have assumed responsibility as editors, without any personal remuneration. After serving as a tremendously energetic Associate Editor for Biotechnology, Dr. Bobbe Ferrailo has changed position and will now share the responsibility as Associate Editor of Pharmacokinetics, Pharmacodynamics and Drug Metabolism with Dr. Robert J. Wills. The new BIOTEC editor is Dr. Randall J. Mrsny, from Genentech, Inc. Welcome on the editorial board, Randy (last name to be pronounced Mursny).

My thanks also extend to the many referees and the editorial advisory board. Without their continuing assistance, the quality of *Pharm. Res.* cannot be assured. In recognition of their work, a list of all referees for October '90 through September '91 was published in the previous issue. (European referees will be acknowledged in the next issue.)

Pharmaceutical Research is continuing to grow, and the page volume for 1992 has been increased to 1632. I am looking forward to another challenging and rewarding year.

Wolfgang Sadée
Editor-in-Chief