

**Alan G.
Marshall**

Biophysical Chemistry

**PRINCIPLES,
TECHNIQUES,
AND
APPLICATIONS**

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Principles, Techniques, and Applications

Alan G. Marshall
University of British Columbia

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To Marilyn, Wendy, and Brian

PREFACE

The object of this book is to provide a *working knowledge* of basic physical chemistry to undergraduates whose primary academic interests lie in the biological sciences, including medicine and dentistry. Most existing texts aimed at a one- to two-semester undergraduate course in "physical chemistry for biologists" are of two types: (1) a mathematically and conceptually diluted abridgement of traditional physical chemistry texts, usually with strong emphasis on small molecules in the gas phase, with perhaps a single short chapter on "macromolecules"; or (2) a loosely connected series of chapters on particular biophysical methods, with strong emphasis on instrumental and practical details at the expense of principles. This textbook attempts to provide the minimal mathematical treatment of physical chemistry that will enable students to *use* their new knowledge to solve relevant biochemical and clinical problems.

The proposed goals call for a new organization of topics. Because most physical chemical techniques are understood in terms of a very few simple mathematical *models*, each of the six major sections of the book introduces a single mathematical model, such as the weight on a spring. The great advantage of this approach is that subsequent application of the *same* model to a variety of *different* biophysical techniques consists simply of changing the names of the mathematical variables. The generality of the approach provides for a natural entry into many modern topics not usually found in elementary texts, including: electron microscopy, "transient" chemical reaction kinetics and "relaxation" phenomena, electrical noise, Fourier methods in diffraction and spectroscopy, and a variety of "absorption" and "dispersion" phenomena. Since each of the six major sections is essentially self-contained (with extensive cross-referencing), the lecturer is free to choose the order of presentation of material according to his or her own taste.

All the material in this book has been class-tested by the author during his eight years of teaching physical chemistry to life science undergraduates at the University of British Columbia. Third-year undergraduates with a year of calculus and a year of introductory chemistry have demonstrated a high level of assimilation of Chapters 1 to 17 in a two-semester course, and more material could be covered by deleting some of the examples. Of course, topics could be deleted for those who would use the book in a one-term course. Problems at the end of each chapter are intended to challenge students, rather than have them "plug" numbers into memorized formulas. (A complete set of solved problems is available as a separate supplement to the text.)

Finally, the text attempts to be current in *modern* biophysical methods. Examples include: "disc" electrophoresis, affinity chromatography, X-ray scattering and diffraction techniques for macromolecules, ion-selective electrodes, circular dichroism, laser light scattering, fluorescence, ultrasonic imaging, and magnetic resonance "spin"-labels. In all cases, subject

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matter has been chosen for its direct biological impact, and student motivation is kept high with frequent modern biochemical and/or clinical applications of the physical results.

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1

THERMODYNAMICS IN BIOLOGY

In general, a complete description of the behavior of matter would begin with *quantum mechanical* analysis of the motion and energy of *individual* atoms and molecules, followed by some *statistical mechanical* (averaging) procedures to provide a description of the behavior of *bulk* matter using *thermodynamics*. (The *rate of change* in properties of bulk matter is described by *kinetics*.) We will shortly encounter the mathematical elements of these various calculations: quantum mechanical mathematics may be developed from generalized *geometry* (Section 5); statistical averages are computed from the mathematics of *chance* (Section 2); and kinetic analysis is based on *calculus* (Section 3). Thermodynamics begins with the study of work and heat. Although the work or heat developed during a process depend on the particular *path* chosen, certain combinations of heat and work are independent of path. Thermodynamic descriptions of bulk matter are thus couched in the mathematics of *exact differentials*, which are simply mathematical objects whose evaluation does not depend on the particular path taken in proceeding from one place to another. The great *abstract* value of thermodynamics is that since the final result of going from one "state" of matter to another often does not depend on the path taken, we need know nothing about the *mechanism* involved along the way. The great *practical* use for thermodynamics comes from the fact that changes in such "state functions" as energy do not depend on the path from one state to another, and, therefore, we are able to equate the end results of proceeding from one state to another by two *different* paths. We thereby often obtain information about reactions that we could not study directly, such as reactions within living cells.

Specifically, thermodynamics is useful for predicting energy changes resulting from chemical reactions, often in cases where the particular reaction of interest is not easily studied directly. Thermodynamics predicts whether or not a given reaction can be expected to occur spontaneously, and how much energy must be supplied to make the reaction occur even if it is not spontaneous by itself—this information is crucial in determining the reaction routes involved in various metabolic sequences. The energies

involved in breaking particular chemical bonds can be computed, and they provide a good measure of bond strength in various molecules. Thermodynamics explains the existence of equilibrium constants and their variation with temperature. Thermodynamics provides detailed information about the mechanism of enzyme-catalyzed reactions, in the sense of identifying the presence of certain intermediates and their associated energy stability. We will be able to account for the difference in pressure across a (semipermeable) membrane that separates a solution of neutral macromolecules from a solution with no macromolecules (osmotic pressure), as well as the difference in electrical potential (Donnan potential) across such a membrane when (charged) ions are present. We will explain the effects of dissolved salt on the solubility of macromolecules, a phenomenon of great practical importance in isolation and purification of proteins. Thermodynamics can be applied to electrochemical cells, so as to produce new types of electrodes that can be made sensitive to the presence of just one type of small molecule in a solution. The occurrence of distinct "phases" (solid, liquid, gas, and others) is readily treated by thermodynamics, and is of modern interest in accounting for the physiological functions of biological membranes at various temperatures, as well as for theories of "pre-biological" evolution of life. Finally, thermodynamics predicts the efficiency of certain types of engines (those that convert heat into work), and provides a suitable framework for discussion of trade-offs in power plant design and operation.

The full formal elegance of thermodynamics becomes evident from a careful orderly development of the first and second "laws" of thermodynamics, and is outside the scope of this discussion, largely because many of the necessary manipulations are most easily illustrated using the ideal gas, whose direct biological applications are limited. We will therefore begin with a brief review of the basic properties of thermodynamic "state functions," and then proceed at once to the biochemical applications. The reader is referred to any of several excellent monographs (see References) for more detailed justification of the basic thermodynamic relations and "laws," which are now presented in most elementary chemistry textbooks.

CHAPTER 1 Work, Heat, and Energy

The science of thermodynamics may be defined as the study of changes in energy of bulk matter and radiation. However, since it is conjectured that the *total* energy of the universe as a whole is constant ("first law" of thermodynamics), it is necessary to limit consideration to a special *isolated part* of the universe, a "system." The term "surroundings" thus denotes the rest of the universe. An "equilibrium" condition is said to apply when the *macroscopic* properties (volume, temperature, pressure, concentration, energy, etc.) of a system are constant with time. A "state" is defined as an *equilibrium* condition for a system. Thermodynamics provides us with a number of useful predictions of what must happen in going from one *state* to another *state*, as in a chemical reaction, phase change, translocation of solvent and/or ions across a semipermeable membrane, flow of electrical current, change in temperature, and the like. We are thus led in a natural way to consideration of "work" and "heat," which are forms of energy "in transit" during such changes in the state of a system.

Work may be expressed as the product of a generalized *force* ("intensive" factor) and a generalized *displacement* ("extensive factor"), as shown in Table 1-1. Because the generalized force can be taken as constant if the generalized displacement is made sufficiently small, it is most fruitful to define the work done over an infinitesimally small displacement, as in Table 1-1. Work is defined as positive when work is done *on* the system (at the expense of the surroundings), and thus is a negative number when the system does work on the surroundings. Finally, the magnitude of work done in going from one state of a system to another depends on the *path* (i.e., the course of the successive small displacements): for a special path for which the system is infinitesimally close to equilibrium throughout the process, the path is said to be "reversible," and the change in any parameter for the process is denoted by lower case "*d*" (e.g., dw for reversible work); for any other path, the ("irreversible") change will be denoted by a " δ " (e.g., δw for work done along an irreversible path).

Two bodies are said to be in "thermal contact" when energy can flow between them but matter cannot. *Heat* is that (energy) which is said to flow from a hotter to a colder body when the two are brought into thermal contact. Various types of heat are listed in Table 1-2, according to their origin. The heat evolved or applied in conducting a chemical reaction is often a good measure of the strengths of the chemical bonds that must be broken and re-formed in the process. The heat required to raise the temperature of a substance gives us a means of predicting the result of a process carried

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Table 1-1 Types of Work (Reversible work, dw , is defined as the product of a generalized force and a generalized displacement)

| dw | = | (generalized force) | · | (generalized displacement) |
|-------------|---|---|---|----------------------------|
| $P dV$ | | P = pressure = force/area | | V = volume |
| γdA | | γ = surface tension = force/distance | | A = area |
| $E dq$ | | E = electromotive force | | q = charge |
| $H d\mu$ | | H = magnetic field | | μ = magnetic moment |
| $F dx$ | | F = force | | x = distance |

out at a temperature different from one at a given temperature—this is especially useful, since most thermodynamic properties of chemical reactions are tabulated for a particular temperature that may be far removed from the, say, physiological temperature of interest. The heat evolved during flow of current (Table 1-2) varies as the square of the current: therefore, since electrical power varies as $(V \cdot I)$, where V and I are voltage and current, it is clear why it is desirable to transmit electrical power at the highest possible voltage in order to minimize heat losses from the passage of current through power lines. Heat is conventionally positive when heat is absorbed by a system. A process is said to be "adiabatic" when no heat enters or leaves the system during the process. Steam engines, the major

Table 1-2 Sources of Heat

| Process of Interest | δq = Heat Required or Generated During Process | |
|--|--|--|
| Raise the temperature of a substance | $\delta q = C \cdot m \cdot dT$, | where C = "heat capacity," m = mass of substance, and T = temperature. |
| Push electric current through a wire | $\delta q = I^2 R dt$, | where I = electric current, t = time, and R = electrical resistance of wire. |
| Change the (physical) phase of a substance (e.g., melt a solid; vaporize a liquid) | $\delta q = h dm$, | where dm is the mass of substance whose phase is changed, and h is the heat required per unit mass of substance ("heat of fusion;" "heat of vaporization") |
| Complete a chemical reaction | $\delta q = h dm$, | where dm is the mass of (say) reactant that is converted to product, and h is the heat required per unit mass of reactant ("heat of reaction"). |
| Overcome friction | $\delta q = F \cdot dx$, | where F is the opposing frictional force and x is the distance over which the force acts. |

present source of power today, act to convert *heat* into *work*. The amount of heat generated during a process also depends on the *path* from initial to final state, as we discuss next.

Although both heat and work for a given process depend on *path*, the first law of thermodynamics states that their *sum* ("energy" of the system) is *independent of path*. In our conventional notation, we would say that

$$dE = \delta q + \delta w \quad \text{First Law of Thermodynamics} \quad (1-1)$$

in which E represents the energy of the system. *Physically*, Eq. 1-1 denies the existence of any device that generates energy with no other net change in the system: if net changes in energy could depend on path, then we could carry out a cyclic process that brought us back to the starting state at a higher energy (say) than when we started. Since no such processes have been found, it is conjectured that none are possible. *Physically*, Eq. 1-1 is based on the idea that

$$\oint dE = 0 \quad (1-2)$$

in which the \oint denotes some (cyclic) path that ends up where it started. *Mathematically*, Eq. 1-2 defines an "exact differential," dE . Equivalently, any exact differential, dF , can be expressed in terms of its independent variables according to

$$dF = \left(\frac{\partial F}{\partial x} \right)_{y,z} dx + \left(\frac{\partial F}{\partial y} \right)_{x,z} dy + \left(\frac{\partial F}{\partial z} \right)_{x,y} dz \quad (1-3)$$

in which the various "partial" derivatives are evaluated as for ordinary derivatives, except that the subscripted variables are treated as constants. For example, for $F(x,y,z) = x^2y^3e^z$, $(\partial F/\partial x)_{y,z} = 2xy^3e^z$. Finally, since it is often particularly convenient to evaluate the heat and work developed for a *reversible* path, and since Eq. 1-1 is valid for *any* path, it is possible to compute the change in energy using

$$dE = dq + dw \quad (\text{reversible path}) \quad (1-4)$$

and the resulting dE will be the same as for *any* chosen path.

Clausius in 1850 proposed a second "state function" (i.e., an exact differential). By breaking down an arbitrary cyclic path into infinitesimally small reversible steps, and working with an ideal gas to keep the calculations simple, it could be shown that

$$\oint (dq/T) = 0 \quad \text{Second Law of Thermodynamics} \quad (1-5)$$

in which the dq notation indicates that any one infinitesimal step is reversible, and T represents (and may in fact be used to define) absolute