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Practical limitations on the use of thermodynamic data from isothermal processes

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Abstract

Enthalpy, entropy and volume data obtained for processes studied in aqueous solvents generally have been assumed to apply to the solute process without consideration of the coupling between the process and the two-state equilibrium of water. Walrafen's confirmation of the latter in 1983 shows that long-debated model to be correct so the enthalpy and entropy contributions to a free-energy change to give unambiguous information must be corrected for the water contribution. The situation is further complicated by differential chemical interaction of amphiphilic solutes with the two water species since experimental complications make correction difficult or impossible. A more general source of error in isothermal experiments is the linkage to the thermal-equilibrium device. That thermal problem discovered only in 1967 is not yet treated in textbooks although it is always a complication in isothermal processes and responsible for a hierarchy of thermodynamic quantities with different levels of reliability. Major consequences for several familiar thermodynamic and extra-thermodynamic methods are examined in terms of relative reliability. In most cases the thermal corrections are restricted by changes in phase state on cooling.

Keywords: Thermodynamic; Errors and corrections; Water two states; Heat; Aqueous mixtures; Hydrophobic hydration

1. Introduction

In 1892, Röntgen proposed that water must have two species [1]. He had been especially struck by the density behavior at temperatures just above 273 K and suspected that there is residual icelike species with low density that melt off just above the freezing point. For the following eighty years opinions for or against his proposal dominated research on water often with favorable results since the rigor and accuracy of many physical–chemical techniques both experimental and theoretical were much improved. In fact it is largely as a result of the high polish Walrafen and coworkers brought to quantitative raman spectroscopy [2] that we can now be certain that Röntgen was correct. It follows then that significant chemistry knowledge deduced from reactions in aqueous media may be wrong. Most free-energy information is likely to remain uncomplicated but enthalpy, internal energy, entropy and volume data are generally suspect since rarely have they been analyzed so as take the two-species of water into account. Primary-bond chang-

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es in small molecules are not severely compromised but processes of large 'soft' molecules like rubbers and proteins present serious and often intractable problems. The necessary corrections would seem to be available by application of straightforward thermodynamic methods but in many cases that is not possible. A major objective of this contribution is to show why and when that is true.

Worley and Klotz in 1966 [3] reported sharp isosbestic point in infrared spectra to be followed by the raman isosbestic points of Walrafen and coworkers. These people established sharp isosbestic points at three frequencies using several spectra from which the standard enthalpy difference between the two states was found to be 10.5 ± 0.5 kJ/mole of formula weight. The standard entropy change depends on the model but assuming 1:1 interconversion stoichiometry it is approximately 28.2 J/Kmole of formula weight. Walrafen et al. [4] cited 10 reports of that enthalpy value obtained from 6 different kinds of experiments and there are three additional confirmations using the very accurate heat-capacity data. With the constant-pressure heat capacities Benson and Seibert [5] and Stey [6] found two states and only two states separated at 298 K and 1 atm by 9.6 kJ/mole of cooperative unit for the enthalpy difference and Chen [7] with the constant-volume data found 9.6 kJ/mole of cooperative unit for the internal-energy difference consistent with the [8] PV difference. Stey and Chen also showed that mercury, benzene, methanol and ethanol have single-peak probability density distribution functions for enthalpy and internal-energy, respectively. Thus far among ordinary pure liquids only water has been found to have more than one macrostate and it is sharply limited to two. In pure water the second predominates only in the supercooled region but it is the basis of the solubility behavior of amphiphiles at higher temperatures as well [9].

These results confirm the two species nature of water but do not give unique descriptions of the two species. Frank and Wen [10] envisioned as the lower-density species, *L*, small 'flickering clusters' of several molecules coupled together by coordinated inductive electron redistributions. If so, the higher-density species, *H*, and lower-density species *L* must have different electronic Hamiltonians and thus different wave equations with different solutions. Thus, the two-state model requires that the two species be chemically different. Benzinger later showed (vide infra) that those differences are the minimum requirement for two or more macrostates [27]. Most proposals for the two states fail because they include only rearrangements of hydrogen bonds without major change in electron distributions about the oxygen atoms. The hydrogen bonds in the *H* species are thought to be electronically identical forming a homogeneous 'random-connectivity' phase with much rapid H-bond bending. Then the *L* species is a local transient formed by cooperative changes in length and stiffness of the hydrogen bonds in local clusters of water molecules with almost no breaking and making of hydrogen bonds in relaxation times estimates as 0.5 ps at 298 K [11]. To explain the lower enthalpy and entropy of the *L* species on average the hydrogen bonds must be stronger, shorter and stiffer freeing up volume used for bending responsible for the higher entropy in the *H* species.

Oguni and Angell [12] showed that hydrazine and hydrogen peroxide were almost identical in their ability to destroy the cooperativity in water responsible for its large heat capacity especially large in the supercooled temperature region. Lumry et al. using the data from Angell found the suppression was produced by one molecule of hydrazine per four or five water molecules [11]. The special features of water depend on the equivalence of the numbers of donor and acceptor sites so the inhibiting effect of hydrazine is due to its 4:2 ratio and that of hydrogen-peroxide to its 2:4 ratio. Such structure-breaking additives also destroy the random-connectivity of H water but at higher mole fractions. This 'geometric relaxation' process as a transient fluctuation without rearrangement of the hydrogen bonds tales place with almost no cratic entropy change The cooperative unit building block in both species is thus a local collection of four or five water molecules so the relaxation enthalpy change of 10.5 kJ is for 4 or 5 moles of water rather than one. For cooperative processes the unit of the mole is the entire cooperative unit. Protein melting is a good example since the ther-

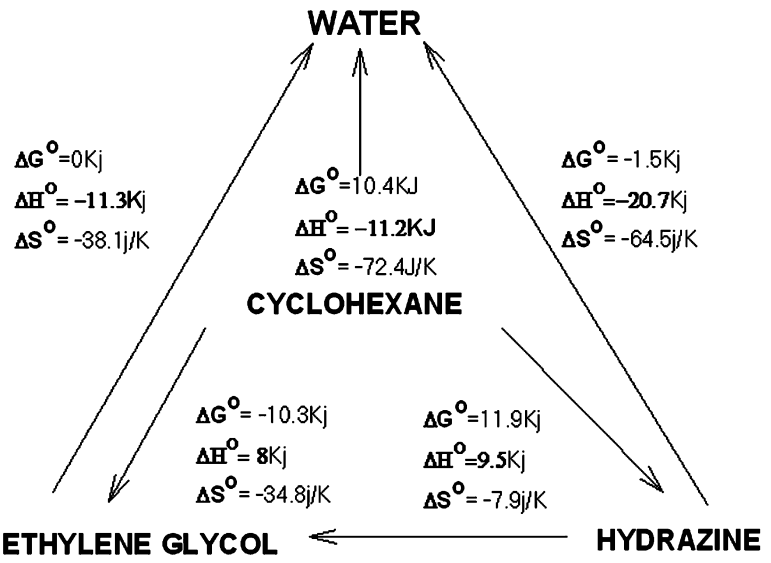

Fig. 1. Solubility of argon in several solvents. 'Hydrophobic hydration' is illustrated by the transfer from cyclohexane to water. 'Inhibited hydrophobic hydration' a la Frank is illustrated by transfer from cyclohexane to hydrazine and the path on the right is transfer from inhibited water to normal water Frank proposed (see text).

modynamic changes are due to 1 mole of cooperative unit, usually a major fraction of the total protein, and not to the many moles of amino-acid residues. On a per mole of water basis the standard enthalpy difference between the two water species is then approximately 2.5 kJ. The enthalpy change in transfer or argon to water of 20.7 kJ at 298 K (Fig. 1) is attributable either to clustering of 8 or 9 water molecules or to an average of 18 in *L* water and 0 in *H* water as follows from the fact that the free energy difference between the two forms is zero near 298 K. The second may not be correct but it is attractive because the most common ice clathrate structure is the pentagonal dodecahedron with its 20 water molecules.

Supercooled water becomes almost pure *L* species as temperature falls toward the unique −45 °C temperature and viscosity and thermodynamic criteria show the small clusters fuse into an increasingly wide variety of larger clusters as temperature is lowered. Larger clusters have only small improvement in free energy possibly due to the critical-point entropy decrease as frequently postulated for the −45 °C special limit temperature of supercooled water [12].

Additional molecular information comes from solubilities of non-polar solutes like argon as illustrated above. Frank suggested that hydrazine might be a good model for 'inhibited water' by which he meant water without solubility anomalies. Following this suggestion Lumry, Battistel and Jolicoeur [9] showed that the solubility difference for non-polar groups, often called hydrophobic hydration, is due to the clustering in the *L* species; 'hydrophobic hydration' does not take place in hydrazine. The rigidity of the *L* clusters makes available free volume for non-polar groups which in turn stabilizes the cavities. The structure-breakers hydrazine, hydrogen peroxide and urea at mole fractions of approximately 0.25 and higher completely eliminate the clusters producing a strongly associated liquid like pure hydrazine, etc. The non-polar additives called structure makers are found at the other end of the Hofmeister series. Sulfate ion and polyethylene glycol are noteworthy examples much used to crystallize proteins because they sequester water. In aqueous mixtures of ethylene glycol or ethanol at 0.08 mole fractions there is no free water [13]. That saturation effect was discovered by Arnett and McKelvey in the very

anomalous heat capacities of mixtures of water with amphiphiles [14].

Aqueous mixtures are generally treated as simple mixtures of water with cosolvents. The effects of cosolvents on proteins are attributed to specific interactions between the cosolvent and protein neglecting the modifications of water produced by the cosolvents. Thus, the stabilizing effect of glycerol and many polyhydroxy compounds well known for proteins and some other kinds of food is due to the decrease in free-water concentration and not to direct interactions of protein with the cosolvent. The effects of these compounds extensively studied by Timasheff [15] and Winzor [16] and their respective coworkers can be formally described as effective in reducing water at protein surfaces because of a classical excluded volume effect. However, a more accurate explanation now possible seems to be that they actually use up water in weak clathrate like cages so very little is available to hydrate groups in the protein–solvent interface. Each cosolvent molecule has a water shell stabilized by weak chemical interaction between cosolvent and lower-density water clusters in a composite of clathrate effect and hydroxyl hydration. The high viscosity of glycerol–water must be due primarily to these interactions rather than direct chain coupling of glycerol molecules as it usually proposed. Somewhat similarly the very unusual properties of dilute solutions of polyethylene glycol polymers is probably due to the fact that the water cages just fit between ether oxygen atoms. As for the proteins the large surfaces to volume ratios require a large number of water molecules and will contract to reduce the surface as the availability of water decreases. Hydration is a major factor is determining protein properties so increasing interfacial free energy forces contraction and the reduction in protein free volume raises thermal stability. Enzymes and several other functional kinds of proteins depend on expansion–contraction of their matrices apparently to provide transient pulse of potential energy to activate substrates [17,18]. That function depends on amount and mobility of matrix free volume so it is very dependent on hydration but at yet the necessary details remain unknown. Lüscher and coworkers [19], showed using the compensation behavior of the hydration process that in free chymotrypsin the matrix free volume is determined by the degree of hydration (compensation temperature 470 K). When the strong inhibitor bromthymolblue was bound, that dependence disappeared probably because no further matrix contraction was possible. Water uptake was restricted to passive surface regions (compensation temperature 290 K) and its total though less tightly bound was considerably larger. The effect of this inhibitor is thus similar to the effect of adding glycerol to the solvent and reflects another feature of the unique expansion–contraction process of protein matrices.

To understand such phenomena one must turn to the cosolvent–water interactions rather than the cosolvent–solute interactions. Thus, as also shown by Timasheff and coworkers structure breakers increase the amounts of free water and favoring expansion and denaturation. In the following the several kinds of possible errors due to linkage of protein conformation to water are discussed in their own right and as an introduction to a more general source of error in isothermal processes of all kinds.

One major class of complication in aqueous mixture of amphiphiles generally unfamiliar is micelle formation. Most amphiphiles form micelles in water even at high temperatures and the critical-micelle concentrations (CMC) of larger surfactants no larger than butanol are often so low that the micelle-free phase is too low for most studies, this property of amphiphiles–water mixtures has been known for many years before Roux and Desnoyers quantified it [20]. Ramadan and coworkers showed how micelle properties change with increasing concentrations of hydrazine [21]. Micellization is a useful model for protein–solvent interactions but not one that can be explored in this contribution.

2. Linkage to water without chemistry

Whatever the stoichiometry and molecular description of the clusters in pure water, there is a general need to correct enthalpy, volume and entropy values for processes in water for their linkage to the two-state process of water. In the simplest linkage model because of the constraint imposed by the equivalence of the chemical poten-

tial of the two species H and L, that process remains at equilibrium during the advancement of the solute process. The two fractions are f_H and f_L.

$$\mu_L = \mu_L^o + RT\ln f_L = \mu_H = \mu_H^o + RT\ln f_H$$

Solute components alter the volume available to the water species thus changing species concentrations and intermolecular potentials both of which alter the standard chemical potentials μ_L^o, μ_H^o. At constant T and P there is no contribution to the free-energy change due to solute process but changes in H, S and V occur as the ratio of L and H water change. This is the simplest view of the complications arising from two rather than a single water state. Although Klotz Ben-Aim [22] and Grunwald [23,24] have given detailed discussion of the consequences; they did not considered the possible ways to evaluate the contributions from the water process to the enthalpy and entropy changes. That is now possible using the species descriptions in pure water and some method to measure their changes with solute process. The special effects of water can be eliminated by using hydrazine or hydrogen-peroxide mixtures with water. The choice depends on the oxidation–reduction propensities of the solutes under study but either cosolvent at mole fraction 0.25 completely suppresses the L species with minimum experimental hazard. This use of 'inhibited waters' suggested by Frank is illustrated by the data in Fig. 1 and was used to analyze the solubility thermodynamics of argon as a typical hydrophobic solute [9]. Urea with a 4:2 ratio of donor to acceptor sites is chemically less complicated than hydrazine and hydrogen peroxide. Frank and Franks [25] found its mixtures with water to be very similar to hydrazine–water mixtures. Including suppression of the L state of water at 0.27 mole fraction (8 mM urea). Most of the vast literature on urea effects on proteins has been interpreted as though the effects are due to direct interaction of urea with protein and the indirect effects are generally ignored although they may be the more important.

3. Linkage to water with chemistry

Frank and Evans in their famous 1945 papers [26] recognized that there is more to the story than the simple case. That permanent gases, other hydrophobes and most amphiphiles become increasingly soluble as the temperature is lowered is one of the special properties of water that suggested to them that there is a chemical interaction between such solutes and water. Now that the two-state description is established that interaction can be seen to be required. With only one water state the poor solubility of hydrophobic species could be attributed to induced hydration clustering as suggested by the large negative entropy changes on immersion of amphiphiles. This remains the most commonly held explanation but Shinoda and Fujita reasoned otherwise and Frank's inhibited water suggestion led to confirmation of the two-state explanation of icebergs as a general concept if not an established molecular description. The distinctions are illustrated by solubility data for argon in water, hydrazine, ethylene glycol and cyclohexane shown in Fig. 1.

The transfer from hydrazine to water models the transfer from Frank's inhibited water to water and shows at 298 K that the standard free-energy change in both solvents is due to a net positive enthalpy change also explains hydrazine as a solvent at that temperature. However, cooling enhances argon solubility in water but not in hydrazine so there must be a source of free energy in the interaction of such solutes with water, a chemical interaction. This is the basis of the Frank–Evans 'iceberg' and it is the favorable factor in 'hydrophobic hydration' [25]. Most of the decrease in the hydrophobic-hydration entropy takes place in formation of the L species from the H species and is offset in the free-energy change at 298 K by part of the negative enthalpy change. The positive part remaining in the hydration of argon is a chemical consequence of the change in potential energy between argon and bulk water. That reaction field is weak as opposed to that in bulk water. Icebergs need not have strict stoichiometry but for this discussion the iceberg can be assumed to have a fixed number of water molecules, n_{LC}.

$$dG=\mu_H dn_H+\mu_L dn_H+\mu_{LC} dn_{LC}$$

$$\mu_{LC}=\mu_L+\mu_C$$

Only L reacts with the solute C in this model and $\mu_H=\mu_L$. The water total w for unit stoichiometry is $n_H+n_L+n_{LC}=w$.

Using concentrations the simplest reaction scheme is

$$H+C\leftrightarrow HC \quad K_H=\frac{[HC]}{[H][C]}$$

$$L+C\leftrightarrow LC \quad K_L=\frac{[LC]}{[L][C]}$$

$$L\leftrightarrow H \quad K_w=\frac{[H]}{[D]} \quad [H]+[L]=W$$

$$K_{\text{app}}=\frac{\left([HC]+[LC]\right)}{\left(\left([H]+[L]\right)\right)[C]}=K_H+(K_L-K_H)\frac{[L]}{W}$$

with which the size of C can be varied; the stoichiometry of L and H with C can be varied as can the proportion of water in L or H form. With careful selection of the sets of reacting conditions or species each variation can be made to produces a linear enthalpy–entropy compensation relation from which the compensation temperature can be determined. Such experiments are useful for discovering the linked process responsible for compensation behavior and in complicated linkage systems they provide a means for quantitative description. When the concentrations of the water species can be determined as by raman spectroscopy, the overall thermodynamic changes can be corrected for the water contributions. However, there are severe complications arising from the isothermal constraint on the measured process applicable to any isothermal process. It can now be shown how that constraint arises.

4. Linkage to a thermostat

The constraint arising from the equality of the chemical potentials of H and L during changes in the solute process of interest adds unknown contributions to total enthalpy and entropy changes. In the chemical case of the previous section there are contributions to the total free energy changes. These make the gross experimental values of the thermodynamic changes unreliable as sources of information about the solute process. The equilibrium constraints discussed in the previous sections are the common explanation for the appearance of linear-free-energy and compensation behavior but the thermal equilibrium constraint is the basis for the most common occurrence of those phenomena. Benzinger discovered this error in 1967 [27], but even now it is not discussed in textbooks despite its ubiquitous effects on use of data from isothermal processes. It rests on no more than integration of the total entropy expression by parts as shown in the Appendix and can be easily rationalized by application of Carnot' expression for the efficiency of a heat engine. The underlying molecular basis is best illustrated by the statistical–mechanical derivation developed from the following derivation using the conventional thermodynamic box [18].

The system is closed, contains only single species α initially and only β in the final state. Both are crystalline from the temperature of interest T down to 0 K. For the constant volume case the Helmholtz free energy A is the center of the development. The internal energy of a system at 0 K is determined calorimetrically from constant-volume heat-capacity data measured as a function of T down to 0 K. The entropy expression is obtained by integration of $\int_0^T \frac{C_v(T')}{T'}dT'=S(T)$. Since $\left(\frac{\partial A}{\partial T}\right)_v=-S(T)$, the thermodynamic 'box' relating the change in Helmholtz work for the isothermal process $\alpha\leftrightarrow\beta$ at T to the energy change at 0 K, $E_{0,\beta}(0)-E_{0,\alpha}(0)$, is (eq) 1.

$$\begin{array}{ccc} \alpha(T) & \xleftrightarrow{\Delta A(T)} & \beta(T) \\ \downarrow & & \uparrow \\ -\int_T^0 S_\alpha(T')dT' & & -\int_0^T S_\beta(T')dT' \\ \downarrow & & \uparrow \\ \alpha(0) & \xleftrightarrow{\Delta E_0(0)} & \beta(0) \end{array} \qquad (1)$$

The overall expression for $\Delta A\ (T) = (A_\beta - A_\alpha)$ is then Eq. (2)

$$\Delta A(T) = \{\Delta E_0(0)\} - \left\{\int_0^T \Delta S(T')dT'\right\} \tag{2}$$

This completes the derivation since it establishes that to make the expression for $\Delta A\ (T)$ in Eq. (2) consistent with the conventional definition of A an integral $\Delta Q(T) = \int_0^T \Delta C_V(T')dT'$ must be added and subtracted from the right side of Eq. (2) to give Eq. (3).

$$\Delta A(T) = \{\Delta E_0(0) + \Delta Q(T)\} - \left\{\int_0^T \Delta S(T')dT' + T\frac{\Delta Q(T)}{T}\right\} \tag{3}$$

$$\{\Delta U(T)\} \quad - \quad \{T\Delta S(T)\}$$

In the latter $\Delta E_0\ (0)$ is the difference between the energies of the first eigenstates and $\Delta Q\ (T)$ is the difference between the mean energy at T and $\Delta E_0\ (0)$. It is an average over fluctuations in energy and usually called the heat. That term is used in different ways and might be confusing. It is not a state function in irreversible processes and although our discussions apply only to reversible processes we shall call it the 'thermal energy'. The sum of the change in potential energy and the zero-point vibrational energies are directly related to the work. Those in thermal energy and entropy have no connection with work changes. Any engine doing work at constant temperature exchanges thermal energy and thermal entropy with the thermostats but the Carnot heat-engine efficiency factor establishes that thermal energy cannot be converted to work when both thermal reservoirs are at the same temperature.

To make these deductions more obvious one turns to statistical mechanics for the molecular bases of thermodynamic expressions. A simple but entirely general statistical–mechanical derivation [18] is easily developed with the Helmholtz (free) energy expressed in terms of the constant-volume Boltzmann partition function, *p.f.*

$$A = -\kappa T \ln \sum_i^\infty e^{-E_i/\kappa T} = E_0 - \kappa T \ln \sum_i^\infty e^{-(E_i - E_0)/\kappa T} \quad :\text{Set}\left(\sum_i^\infty e^{-(E_i 0)/\kappa T}\right) = p.f. \tag{4}$$

$$\left(\frac{\partial(A/T)}{\partial(1/T)}\right)_V = U = E_0 + (p.f.)^{-1}\sum_i (E_i - E_0)e^{-E_i/\kappa T} \quad \text{and} \tag{5}$$

$$\left(\frac{\partial A}{\partial T}\right)_V = -S = -\kappa \ln \sum_i e^{-(E_i - E_0)/\kappa T} + (p.f.T)^{-1}\sum_i (E_i - E_0)e^{-E_i/\kappa T} \tag{6}$$

The last term in each is the average energy fluctuation conventionally called heat and heat entropy, respectively but labeled thermal quantities here. On reforming A from $A = U - TS$ the heat terms cancel: to yield $A(T) = E_0(T) - \kappa T \ln \sum_i e^{-(E_i - E_0)/\kappa T}$ in which E_0 is the potential energy plus the zero-point vibrational energies and the sum term is the degeneracy weighted for T. The thermal terms have disappeared. That their disappearance by mutual cancellation has not been obvious is due to the historical accident that entropy is not routinely written in terms of the degeneracy term and the thermal term (cf. Appendix A). These differ just as potential energy and thermal energy differ. The latter are lumped together in the internal energy, U, because of first-law conservation but they are very dissimilar the heat being at maximum entropy at the prevailing temperature and the potential energy having only the degeneracy entropy. Thermal energy is kinetic energy totally disordered and potential energy is not disordered at all. Potential energy gives the total of energy available for thermal-energy production and degeneracy entropy describes the maximum number of ways that can occur. The latter

Table 1
Entropies of formation at 298.15 K in j M^{-1} K^{-1}; taken from Lewis and Randall [8]

Metal	S (total)	S (thermal)	S (motive)	S (the)/S (mot)
Cesium	84.5	25.9	58.2	0.31
Lead	63.6	22.6	41.0	0.36
Gold	49.0	20.1	28.5	0.42
Copper	33.9	16.7	17.2	0.49
Chromium	23.9	13.8	10.0	0.58

might also be called the capacity of the system. Together they give the total thermal energy possible at the system temperature and that is equal to the negative of the Helmholtz free energy as shown explicitly by the partition function. In reversible isothermal processes change in the potential energy are just balanced by change in the entropy factor For example, in using an electrochemical cell as the system to do reversible work on some coupled system, another cell for instance, thermal energy flows in or out of the cell into the thermostat at constant *T* but cannot contribute to the work being done. That this is no more than the Carnot efficiency factor for thermal-energy transfer between two thermal reservoirs at the same temperature has often escaped attention. The analogy with the linkage of a solute process to the two-state process of water always at equilibrium rests on the same kind of argument. Since the thermal-equilibration process at constant temperature is always at equilibrium, it cannot contribute work. To do so would cause spontaneous flow of heat from cold to hot thermal reservoirs.

In any process carried out at constant temperature changes in *H* or *U* and *S* are usually ambiguous although the error in equating their parts in ΔA (*T*) to their totals may not be large. Primary-bond rearrangements in the gas phase are important examples of the latter and may explain why the thermal complication was overlooked. Proteins and soft or rubberlike macromolecules are at the other end of this spectrum where those complications can dominate the totals of *H* and *S*.

Frank called the potential energy and degeneracy changes that make up *A* or *G* 'motive changes' after Carnot. As observed above, the conventional thermochemical procedure for determining the motive changes is the measurement of heat capacity from a temperature of interest to 0 K but that is appropriate only for crystalline solids that do not change phase in the cooling process. Metals are among the few examples and the separations of the entropy for several metals are given in Table 1. Rhodes showed that even these values are somewhat deceptive because major parts of the differences are due to differences in vibrational frequencies and thus at any lower temperature vary as a system approaches the classical limit. The differences are thus quantum-mechanical in origin providing Rhodes term 'quantum thermodynamics' [28].

5. The three-level hierarchy of thermodynamic quantities: [29,30]

Free energy (Gibbs and Helmholtz) contains only motive quantities and as a result is reliably related to work but contains only a minimum of information about the responsible process.

Enthalpy, entropy, internal energy and volume are composite quantities rarely separable into quantitative values of motive and thermal parts (vide infra) and thus usually of ambiguous information content.

Heat capacity, compressibility and their higher *T* and *P* derivatives describe the probability-density distribution function of the enthalpy in terms of the orthogonal set of temperature moments. For systems in single electronic states the pdf is strictly thermal and would provide full descriptions of heat if all the moments were available. The few experimentally available moments may dominate the enthalpy pdf for these single-state situations and can be used to estimate the thermal energy. Complications arise when more than one electronic state is accessible, since the heat capacity then

contain a 'between-states' term that can dominate the aggregate of single-species heat capacities. That term contains the square of the total enthalpy difference between electronic states and thus contains motive changes as well as thermal-energy changes. It is usually the device by which total enthalpy changes are computed from temperature-dependencies as with Walrafen's raman data. The higher moments also contain between-states contributions and are equally ambiguous as a result.

6. Some consequences of the motive-thermal dichotomy

1. When the thermal terms are appreciable, fractions of total H or U and S change in series of related processes the ratio of enthalpy to entropy change tends toward a positive constant approximately equal to the mean experimental temperature. This parallelism becomes more exact when the thermal parts become larger than the motive parts. This behavior is very common and usually attributed to systematic chemistry as in Hammett's $\sigma\rho$ linear-free-energy behavior but the thermal basis is more common and can often be tested by the temperature dependence.
2. Since motive quantities must change in both systems it is not possible to transfer free energy from one system to another at constant temperature without change in the electronic Hamiltonians of each. Although vibrational zero-point energies and concentration factors in entropy are motive quantities, all excited states are thermal energy and useless for free-energy exchange at constant temperature. This is the criterion that defines thermodynamic macrostates.
3. Rate processes adequately treated by Absolute rate theory or Kramers rate theory are subject to the same restrictions on total activation enthalpy and entropy as normal equilibrium processes. Item one in this list applies. Activation free energies are reliable but not equal to true thermodynamic free energies because the degree of freedom including the reaction coordinate has been used for the time-dependence. The Eyring–Leffler–Hammond 'principle' [30] for comparison between activation free energy in a rate process and the standard free energy change to estimate progression along the reaction coordinate is not jeopardized so long as it is applied to free energy. Because the enthalpy has no quantitative relationship to the free energy, it cannot be used as a substitute.
4. Tables of bond energies computed using total enthalpy changes cannot be accurate since they contain thermal parts that have no relevance for the potential energy that determines bond strength. However, bond-rupture quantities computed from gas-phase enthalpy data have small errors from equating total change to motive enthalpy change.
5. Benzinger's discovery provides a general explanation and formal structure for the extrathermodynamic relationships known as linear-free-energy behavior and its associated enthalpy-entropy compensation relationship. The developments are given in our second contribution to this issue.

An important procedure that remains unchanged is the much-used test for dominance of entropy versus entropy in determining a free energy change. The relationship between the conventional test ratio $\frac{\Delta H}{T\Delta S}$ and the correct one $\frac{\Delta H_m}{T\Delta S_m}$ is

$$\frac{\Delta H}{T\Delta S}=\frac{\frac{\Delta H_m}{T\Delta S_m}+\frac{\Delta S_t}{\Delta S_m}}{1+\frac{\Delta S_t}{\Delta S_m}}.$$

The two ratios are not equal but their corresponding inequalities are the same since adding a quantity to both sides of an inequality does not change the inequality.

7. Motive and thermal parts of entropy and entropy are usually not experimentally determinable

Direct evaluation of thermal or motive enthalpy at a temperature of interest is rarely possible and may never be. The usual calorimetry experiment measures the total enthalpy plus free energy by irreversible conversion of free energy to thermal

energy. By using a scanning calorimeter the total free energy change is given by the double temperature integral but single integration gives the total enthalpy The integral over the heat capacity down to 0 K. gives the motive enthalpy at 0 K but it is the motive enthalpy and at some higher temperature that is necessary but as shown below, one is not obtainable from the other is there is a change of state on cooling. The complication arises because of the propensity of real substances other than crystalline solids to change phase at some temperature on cooling to 0 K It is the resulting change in electronic Hamiltonian and thus in the Schrödinger equation that is the culprit rather than any failure of thermodynamics. In all phase changes including the pseudo-first-order changes in protein matrices on which their function depends the motive parts undergo large changes that cannot be estimated with any accuracy. The separation can be estimated for very simple systems by theory but the larger thermal errors occur with soft materials like polymers and proteins for which accurate computations are rarely possible. This is illustrated with the example below.

7.1. Source of uncertainty

If there is a change in state, as $\alpha(T') \leftrightarrow \alpha'(T')$ in the diagrammed process below, the two cooling steps apply to two different chemical systems, α at temperatures above T' and $\alpha'(T')$ down to 0 K.

$$\begin{array}{ccc}
\alpha(T) & \xleftarrow{\Delta A_{\alpha\beta}(T)} & \beta(T) \\
\downarrow & & \uparrow \\
-\int_T^{T'} S_\alpha(T')dT' & & -\int_0^T S_\beta(T')dT' \\
\downarrow & & \uparrow \\
\alpha(T') & \xleftarrow{\Delta G_{\alpha\alpha'}(T')} \alpha'(T') & \uparrow \\
 & \downarrow & \uparrow \\
 & -\int_{T'}^0 S_{\alpha'}(T)dT & \uparrow \\
 & \downarrow & \uparrow \\
 & \alpha'(0) \xleftarrow{\Delta E(0)_{\alpha'\beta}} & \beta(0)
\end{array} \qquad (12)$$

In this thermodynamic box the $\alpha \leftrightarrow \alpha'$ process is the solidification of liquid α at its melting point T'. The standard free energy change is zero. As usual $\Delta H_{\alpha\alpha',t} = T'\Delta S_{\alpha\alpha',t}$ and at the melting temperature $\Delta H_{\alpha\alpha',m} = T'\Delta S_{\alpha\alpha',m}$ but neither side can be evaluated. Further cooling to 0 K will yield $E_{\alpha'}(0)$ but that applies to the frozen system at 0 K and not to the liquid system at T. As with any chemical change, any phase change is a change in Hamiltonian, which in turn always causes changes in the values of motive parts. Melting and evaporation have large motive contributions because many vibrational modes change in number and in characteristic frequency. As a result phase changes eliminate the calorimetric approach to the separation problem A well-known example is the comparison of rhombic and monoclinic sulfur possible because the monoclinic form was maintained as a metastable solid from the phase-transition temperature 368.5 to 0 K. Assuming the entropies of both phases to be zero at 0 K, the motive enthalpy and entropy changes at 368.5 K are 164 J/M and 0.42 J/MK, respectively [31]. The thermal enthalpy and entropy changes are 252 J/M and 0.62 J/MK, respectively, thus larger than the motive quantities. The motive changes are the errors that would be made by extrapolation to 0 K as though the rhombic form were the stable phase below 368.5 K as well as above.

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Ernest Grunwald has been a major contributor to modernizing thermodynamics for liquid mixtures and biological applications. We dedicate this work to him in memoriam. I am indebted to Walter Kauzmann for stimulating my interest in proteins from 1942 to the present. Bellevue, WA, Acorn Ventures Inc., 1309, 114th Ave., S.E. 98004.

Appendix A:

1. A thermodynamic derivation of the motive-thermal dichotomy in the entropy:

   Integrate the average entropy change over the range 0 to T by parts

$$T^{-1}\int_0^T \Delta S(T)dT' = \int_0^T \int_0^{T'} \frac{\Delta C_V(T')}{T''} dT''dT'$$
$$= \Delta S(T)$$
$$= \Delta S(T)T - \int T' \frac{\Delta C_V(T')}{T'} dT' \quad \text{(A1)}$$

Rearranging gives

$$\Delta S(T) = T^{-1}\int_0^T \Delta S(T')dT' + T^{-1}\int_0^T \Delta C_V(T')dT' \quad \text{(A2)}$$

The second term on the right is the total thermal-energy change divided by T and is cancelled in ΔA by the corresponding term from $\Delta U(T)$. The first term on the right is the degeneracy defined in the statistical-mechanical proof (vide supra). This development makes Benzinger's discovery obvious and describes the entropy by its physically significant parts.

2. General procedure for separating motive and thermal terms.

Benzinger's discovery provides simple procedures for analyzing even complex systems in terms of their equational forms for the motive and thermal parts of enthalpy and entropy changes. The most useful such procedure involves three steps: (1) Write the complete formal mechanism for the process. (2) Obtain the expressions for total enthalpy and entropy changes in the usual way as temperature derivatives of the free-energy change. (3) Identify the common terms. Those are the generalized thermal parts of enthalpy and entropy change.

For illustration these steps are applied to the transfer of a substance from its ideal gas phase to a mixed liquid with a van der Waals equation of state: $P = \frac{RT}{(V-b)} - \frac{a}{V^3}$. The parameters a and b depend on the composition which for convenience we fix. Only the total volume, V, is temperature dependent in this approximation. The free volume is $(V-b)$. The free energy change [32,33], total enthalpy change and total entropy change are the following, respectively.

$$\Delta G = RT\ln\left(\frac{x_i RT}{V-b}\right) + RT\frac{b}{(V-b)} - \frac{a}{V^2} \quad \text{(A3)}$$

$$\Delta H = -\frac{a}{V^2} - RT + \left[\frac{TR}{(V-b)} + \frac{TRb}{(V-b)^2} - \frac{2a}{V^3}\right]T\left(\frac{\partial V}{\partial T}\right) \quad \text{(A4)}$$

$$\Delta S = -R\ln\left(\frac{x_i RT}{V-b}\right) - \frac{Rb}{(V-b)} - R + \left[\frac{TR}{(V-b)} + \frac{TRb}{(V-b)^2} - \frac{2a}{V^3}\right]\left(\frac{\partial V}{\partial T}\right)_{\text{comp}} \quad \text{(A5)}$$

The motive enthalpy change is a/V^2 and the motive entropy change is $-R\ln\left(\frac{x_i RT}{V-b}\right) - \frac{Rb}{(V-b)}$. These are obtained by removing their common terms since those terms are their thermal parts:

$$\Delta S_t = -R + \left[\frac{TR}{(V-b)} + \frac{TRb}{(V-b)^2} - \frac{2a}{V^3}\right] \times \left(\frac{\partial V}{\partial T}\right) = \frac{\Delta H_t}{T} \quad \text{(A6)}$$

The expression for the thermal entropy is a limited source of information because there are only two parameters. Expressions for the heat-change, compressibility change and the higher P and T derivatives can be extracted from it by successive differentiation but have little physical significance as a consequence of the low-order approximation of this equation of state. However, the procedure illustrated is entirely general. To the extent that the model is an accurate fit to the data the method provides a simple way to estimate the motive and thermal parts [34].

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