Stoichiometry of Hemoglobin Reactions

Thermodynamic analysis shows the effect of aggregation changes on the equilibria involved in hemoglobin reactions.

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One of the most intriguing reactions in biochemistry is that of the oxygenation of hemoglobin (Hb). In principle, the equilibrium between hemoglobin and oxygen should not require any complicated treatment, since it is no more than an addition reaction of the type:

$$pA + nB \rightleftarrows qAB \quad (1)$$

where p, q, and n are the stoichiometric coefficients corresponding to the reactants A, B, and AB. Hüfner (*1*) considered it so. In 1903, Bohr (*2*) showed that when the fraction of oxygenated hemoglobin was plotted against the partial pressure of oxygen, the curve had a sigmoid shape (Fig. 1) rather than the hyperbolic form which would result from a reaction such as:

$$Hb + O_2 \rightleftarrows HbO_2 \quad (2)$$

In order to explain this, other theoretical treatments were developed, the best known of which are those of A. V. Hill (*3*) and Adair (*4*).

Hill (*3*) assumed the following two reactions:

$$n\ Hb \rightleftarrows Hb_n \quad (3)$$

and

$$Hb_n + n\ O_2 \rightleftarrows Hb_n\ O_{2n} \quad (4)$$

Therefore, according to Hill's theory:

$$K = \frac{(Hb_nO_{2n})}{(Hb_n)p_{O_2}^n} \quad (5)$$

where p_{O_2} is the partial pressure of O_2. Simple rearrangements lead to the expression:

$$\text{Percent saturation} = \frac{(Hb_nO_{2n})}{(Hb_n) + (Hb_nO_{2n})} = \frac{Kp_{O_2}^n}{1 + Kp_{O_2}^n} \quad (6)$$

The ample latitude allowed to Hill's equation is shown in Fig. 2. Adair (*4*), however, showed that the molecular weight of hemoglobin is 68,000; hence the number of iron atoms per molecule, and consequently the value of n, should be 4.

Adair himself tried to find a substitute for Hill's theory, and he did so by assuming a set of sequential addition reactions (*4*, *5*):

$$Hb_4 + O_2 \overset{K_1}{\rightleftarrows} Hb_4O_2$$

$$Hb_4O_2 + O_2 \overset{K_2}{\rightleftarrows} Hb_4O_4$$

$$Hb_4O_4 + O_2 \overset{K_3}{\rightleftarrows} Hb_4O_6$$

$$Hb_4O_6 + O_2 \overset{K_4}{\rightleftarrows} Hb_4O_8$$

and by assuming that the values of K_1, K_2, K_3, and K_4 were of increasing magnitude. The resulting equation:

$$\text{Percent saturation} = (K_1p_{O_2} + 2K_1K_2p_{O_2}^2 + 3K_1K_2K_3p_{O_2}^3 + 4K_1K_2K_3K_4p_{O_2}^4)/4(1 + K_1p_{O_2} + K_1K_2p_{O_2}^2 + K_1K_2K_3p_{O_2}^3 + K_1K_2K_3K_4p_{O_2}^4) \quad (7)$$

has been fitted to experimental data, with varying degrees of claimed success (*6*, *7*). Since these equilibrium constants were unequal the hypothesis of heme-heme interaction was postulated. All this has prompted considerable experimental and theoretical work, but the heme-heme interaction theory remains as a hypothesis still to be proven.

Hence it is clear that every one of the hypotheses advanced for the explanation of the hemoglobin-oxygen reaction relies on a given assumed stoichiometry for the process. The question arises whether it is not possible to establish a more inductive approach to this whole problem, namely, whether the stoichiometry itself cannot be determined from the experimental data. In cases where the chemistry of the compounds participating in a reaction is known, it is a common practice to assume a stoichiometry and to attempt to fit it to the experimental data. This is not justified in cases such as the one under consideration, which involves a molecule now known to undergo changes in the state of aggregation under the most varied conditions (*8*, *9*). In fact, one must be careful in such cases to distinguish between an overall thermodynamic reaction and its detailed kinetic mechanism.

Michaelis (*10*) was one of the first to propose a method for the determination of the stoichiometry of a chemical reaction on the basis of the experimental data alone. His method, developed for the treatment of oxidation-reduction reactions, has been recently extended by one of us (*11*) in order to cover changes in aggregation and stoichiometric coefficients, as well as to cover parallel reactions of one or more common reactants, and other complicated stoichiometric schemes. This leads to equations from which the values of p, q, and n in Eq. 1 can be calculated and, also, to experimental tests which may be applied to the data in order to confirm a given type of stoichiometry.

In particular, for a general reaction of hemoglobin with any reactant L:

$$qHb_bL \overset{K'_{obs}}{\rightleftarrows} pHb_a + nL \quad (8)$$

suitable algebraic operations that involve as postulates only those of conservation of mass and conservation of charge and the thermodynamic definition of chemical equilibrium lead to the expression:

$$-\log L = -\log K_{obs} + \frac{1}{n}\log\frac{(1-x)^p}{(x)^q} \quad (9)$$

where:

$$-\log K_{obs} = -\frac{1}{n}\log K'_{obs} + \frac{1}{n}\log\frac{(p/n)^p}{(q/n)^q}(C_{Hb}^o)^{(p-q)} \quad (10)$$

K'_{obs} is the concentration constant for the dissociation reaction with any general ligand or reactant L; p, q, and n are the stoichiometric coefficients of this

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reaction; a and b are the aggregation coefficients of the hemoglobin species; C°_{Hb} is the total concentration of hemoglobin in all forms given in equivalents per liter; and x is the fraction of the dissociation reaction completed (that is, the percentage of reaction). The quantity $-\log K_{obs}$ is therefore dependent upon concentration; hence the whole dissociation curve is shifted along the log L axis and does not change in shape upon dilution. On the other hand the shape of the curve is only dependent upon the relative values of p and q.

Equation 9 relates the observed equilibrium constant, K_{obs}, with the concentration of free ligand in solution at any value of x or the percentage of reaction. Examination of Eq. 10 shows that when $p = q$, it reduces to:

$$\log K_{obs} = \log (K'_{obs})^{1/n} \qquad (11)$$

and Eq. 9 becomes equivalent to the Hill formulation, Eq. 5, that is:

$$-\log L = -\frac{1}{n}\log K'_{obs} + \frac{1}{n}\log\frac{(1-x)}{(x)} \qquad (12)$$

Thus, the observed equilibrium constant term of Eq. 9 becomes independent of the concentration of hemoglobin as would be expected from physical considerations. If from Eq. 12 the log L is plotted against x, the resulting curve should be symmetrical about the value $x = 0.5$, while a similarly plotted curve of Eq. 9 should be asymmetric. Moreover, when $p \neq q$ the curves of log L plotted against x, in addition to their asymmetry, will show changes in K_{obs} concomitant to changes in the concentration of hemoglobin.

It is also possible to derive expressions such as:

$$\frac{p}{n} = \frac{1}{2}\left(\frac{|\log L_{10\%} - \log L_{90\%}|}{\log(9/1)} - \frac{|\log L_{10\%} + \log L_{90\%} - 2\log L_{50\%}|}{\log[4(0.1)(0.9)]}\right) \qquad (13)$$

and

$$\frac{q}{n} = \frac{1}{2}\left(\frac{|\log L_{10\%} - \log L_{90\%}|}{\log(9/1)} + \frac{|\log L_{10\%} + \log L_{90\%} - 2\log L_{50\%}|}{\log[4(0.1)(0.9)]}\right) \qquad (14)$$

where $\log L_x$ is the experimentally observed value at x percent of reaction. This permits one to estimate the stoichiometric coefficients p and q directly from the experimental data. Similar expressions may be derived for any complementary set of values of x and $(1 - x)$. However, the values of log L at (10 percent, 90 percent) and (20 percent, 80 percent) reaction are the most convenient values to use in the analysis of published hemoglobin data. We have applied these equations and those for other complementary points to several sets of experimental data on hemoglobin reactions available from the literature, with the results shown in Table 1.

Table 1. Calculation of stoichiometric coefficients of hemoglobin reactions according to Eqs. 13 and 14. The data points analyzed give the complementary sets of values of x and $(1 - x)$ used in each case. Oxyhemoglobin, carbon monoxyhemoglobin, and nitric oxide hemoglobin were the compounds dissociating.

Species	pH	Temp. (°C)	Data points analyzed (%)			p/q	p/n	q/n	Ref.
				Oxyhemoglobin					
Man	7.40	37	2	50	98	1.70	0.541	0.317	*21*
Man	7.40	37	10	50	90	2.05	0.613	0.302	*21*, p. 64
Man	7.40	37	15	50	85	2.03	0.602	0.297	*21*
Man	7.60	37	10	50	90	2.04	0.615	0.302	*21*, p. 74
Man	7.60	37	20	50	80	1.85	0.572	0.309	*21*, p. 74
Man	7.60	37	40	50	60	1.70	0.537	0.315	*21*, p. 74
Man	7.40	30	10	50	90	2.04	0.615	0.302	*21*
Man	7.40	30	20	50	80	1.85	0.574	0.311	*21*
Man	7.40	23	10	50	90	2.02	0.612	0.303	*21*
Man	7.40	23	20	50	80	1.93	0.586	0.303	*21*
Cat	7.40	37	20	50	80	2.15	0.505	0.235	*21*, p. 78
Cow	7.4	38	10	50	90	2.42	0.460	0.190	*21*, p. 80
				Carbon monoxyhemoglobin					
Man	7.8	38	10	50	90	2.33	0.595	0.251	*13*
Man	7.2	38	10	50	90	1.70	0.605	0.355	*13*
				Nitric oxide hemoglobin					
Sheep	9.1	19	20	50	80	1.00	1.91	1.91	*22*

The surprising feature arising from these calculations is that in most cases the ratio of p to q approximates 2.0.

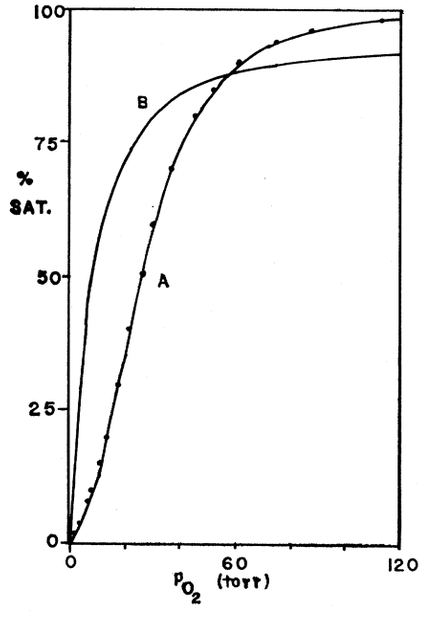

Fig. 1. Dissociation curve of Hb — O_2 plotted as the percentage of saturation against p_{O_2}. Curve A is a sigmoid curve (*21*). Curve B is a rectangular hyperbola obtained from Barcroft (*13*).

Since the molecule of hemoglobin to which these calculations refer contains 4 atoms of Fe, n must be 4, and therefore from Table 1, $p \sim 2.4$ and $q \sim 1.2$. In order to judge the effect of experimental errors upon our conclusions, we have studied the effect of the deliberate introduction of 5-percent error into one set of the analyzed data. The set chosen was that of the second entry in Table 1, in which $p_{O_2} = 8.2$ torr at 10 percent, 26.3 torr at 50 percent, and 61.4 torr at 90 percent, which gives a calculated $p/q = 2.03$. Increasing both the 10- and 90-percent values by 5 percent to 8.6 and 64.4 torr gives $p/q = 1.62$. Decreasing both values by 5 percent to 7.8 and 58.4 torr gives $p/q = 2.62$. Decreasing the 10-percent value by 5 percent to 7.8 torr and increasing the 90-percent value by 5 percent to 64.4 torr gives $p/q = 2.05$. Increasing the 10-percent value by 5 percent to 8.6 torr and decreasing the 90-percent value by 5 percent to 58.4 torr gives $p/q = 2.13$. All other factors considered, therefore, we feel safe in concluding that experimental errors do not seriously affect our calculations. On this basis, the oxyhemoglobin reaction, for example, could with justification be written in a first approximation as:

$$Hb_4O_8 \rightleftarrows 2Hb_2 + 4O_2 \qquad (15)$$

Equation 15 is an expression of an overall thermodynamic reaction and says nothing about the detailed kinetic mechanism. In fact this expression is an absolute prerequisite for the detailed formulation of a kinetic mechanism.

Thermodynamic Cycle

As previously pointed out, when an addition reaction takes place without changes in the state of aggregation of the reactant to which it is referred, p is equal to q, and a plot of the extent of the reaction as a function of the logarithm of the concentration of the ligand, for example, $-\log p_{O_2}$, is a sigmoid curve symmetric with respect to the midpoint. The fact that p is not equal to q would result in asymmetric curves, such as those found for the hemoglobin-oxygen equilibrium (Fig. 3). However, the reaction under consideration is not as simple as written in Eq. 15; if this were so, there would be no deviations of p and q from their theoretical values of 2 and 1. Other pertinent factors must be considered, and they are suggested by the chemistry of hemoglobin in aqueous solutions.

It is now known that both the oxygenated and the deoxygenated forms of hemoglobin can be present as dimers or tetramers of the unit that contains one iron atom. The concentration of hemoglobin, the concentration of salts, and the pH are all factors influencing the extent of the aggregation reaction (*8, 9, 12*).

The dimers and tetramers can be considered to exist in a state of equilibrium that is influenced by the variation of any of the constraints just mentioned, as well as by the temperature. This in turn makes it necessary to consider not only the reaction expressed by Eq. 15, but also the other possible equilibrium reactions between the oxygenated and deoxygenated dimers and tetramers; more specifically:

$$\begin{array}{ccc} & \overset{K'_1}{\rightleftarrows} & \\ Hb_4(O_2)_4 & & Hb_4 + 4O_2 \\ \Updownarrow & \overset{K'_{obs}}{\searrow} & \Updownarrow \\ 2Hb_2(O_2)_2 & \underset{K'_2}{\rightleftarrows} & 2Hb_2 + 4O_2 \end{array}$$

This cycle, also, is an expression of an overall thermodynamic reaction and it says nothing about the detailed kinetic mechanism. This set of thermodynamic cycles or the "box" system includes all the experimentally observed pertinent reactions; the two equilibria written horizontally correspond to the oxygen dissociation reactions of dimer and tetramer, while the two reactions indicated by the vertical arrows are those in which the changes in state of aggregation take place. It is obvious that the diagonal path indicated in the box corresponds to the reaction represented by Eq. 15.

A general equation that takes into consideration all the reactions represented by a general box with unknown aggregation coefficients is:

$$\begin{aligned} -\log L = & -\log K_{obs} \\ & + \frac{1}{n}\log\left\{\frac{[1 - x - K_1 x^{(1-n)/q}(C^o_{Hb})^{-n/q}]^p}{[x - K_2(1-x)x^{n/p}(C^o_{Hb})^{n/p}]^q}\right\} \\ & + \frac{1}{n}\log[1 - K_1K_2(xC^o_{Hb})^{n(1/p-1/q)}]^{q-p} \end{aligned} \quad (16)$$

where all terms have the same meaning as in Eqs. 9 and 10 and where $K_1 = (K'_1)^{1/q}$ and $K_2 = (K'_2)^{1/p}$ for the reactions given in the box. More specifically K'_1 is for the dissociation reaction corresponding to the tetramer species and K'_2 is for the association reaction corresponding to the dimer species. For this system a change in C^o_{Hb} not only shifts the whole curve but also changes its shape as well. Therefore the shape of the curve is dependent on concentration as well as upon the relative values of p and q. Thus, for the condition $K_1 = K_2 = 0$, Eq. 16 reduces to Eq. 9. Conversely, when $K_1 = K_2 = \infty$ the observed reaction becomes the other diagonal of the box. Also, if $p = q = 1$ and $K_1 = K_2 = 0$, then Eq. 16 is reduced to the logarithmic form of Hill's equation. That the values of p and q are not integers when the data obtained for hemoglobin reactions are analyzed in terms of Eq. 9 is a consequence of disregarding the concentration terms which appear in the general Eq. 16. On the other hand, an attempt to derive from Eq. 16 expressions such as Eqs. 13 and 14 which would permit one to estimate the stoichiometric coefficients of the box, leads to intractable mathematical difficulties.

Examination of the experimental results obtained from hemoglobin reactions shows that in the great majority of the cases analyzed in Table 1 there is a considerable degree of asymmetry in the logarithmic plots. The most careful measurements of the oxygen equilibrium also show considerable deviation from symmetry (*7*).

In general, there are three main types of stoichiometric systems for which such asymmetry in graphs of log L against percentage of reaction can be predicted: (i) systems with parallel reactions of independent components (such as an impurity) reacting with a common ligand, (ii) systems with change of aggregation and stoichiometric coefficients of the species being titrated, and (iii) systems of sequential reactions (as postulated by Adair). In the cases under consideration it appears reasonable to rule out type i which implies considering hemoglobin solutions to be free from comparable amounts of other chemical species that bind oxygen (only to within one order of magnitude in concentration). Types ii and iii are distinguishable by studying the effect of dilution on the apparent equilibrium constant of the reaction.

For systems that belong to type ii, Eq. 10 shows that when the total concentration of the titrated species, C^o_{Hb}, is lowered, $-\log K_{obs}$ becomes smaller. Therefore, $-\log L$ in Eq. 9 also becomes smaller, for an identical value of x. This is equivalent to saying that the concentration of the ligand necessary to reach the same degree of saturation diminishes with dilution, as if an increase in the affinity of the titrated species for the ligand had occurred. Now this is precisely what happens with hemoglobin; there is an apparent increase in its affinity for oxygen with dilution (*13*). Furthermore, dilution causes a change in the dissociation curve, plotted as percentage of saturation against p_{O_2}, which in dilute hemoglobin solutions tends to be hyperbolic rather than sigmoid in shape (*13*). When the logarithm of the partial pressure of the gaseous ligand is plotted against the fraction of reaction, the dissociation curve is always sigmoid, but upon dilution the usual asymmetry tends to vanish. Therefore a right hyperbolic curve, obtained when the percentage of saturation is plotted against p_{O_2}, corresponds identically with a symmetric sigmoid curve obtained when the log p_{O_2} is plotted against the percentage of saturation (Figs. 1 and 3). Thus, the dilution effects observed in hemoglobin reactions are consistent with changes in aggregation.

On the other hand, these effects are not predicted by Eq. 7 which represents the sequential reaction system. This is obviously clear from the fact that there are no concentration terms in Eq. 7. A graph of the logarithm of the ligand concentration plotted against the fractional saturation will be asymmetric if $K_1K_4 \neq K_2K_3$ (*7*); but neither the asymmetry nor the apparent affinity should be affected by the concentration of the titrated species.

There are other factors supporting a system with changes in aggregation for hemoglobin reactions. Increase in

salt concentration causes a change in the asymmetry of the curves of log L plotted against the percentage of x concomitant with an apparent increase in affinity for oxygen (*13, 14*); but, simultaneously, high salt concentrations move the equilibrium between dimers and tetramers toward the former, both in reduced and in oxygenated hemoglobin (*8, 12*). These facts are hard to reconcile with the sequential reaction system, which should require exactly the opposite situation; since the best fits of experimental data for this system show that K_4 is considerably larger than K_1, K_2, and K_3 (*7*), the apparent increase in affinity should be reflected in an increase in K_4. To have K_4 operating in this fashion requires that the predominating molecular species should contain four iron atoms, while experimentally this increased "interaction" corresponds to a decrease in the proportion of tetramer.

On the other hand, the system with change in aggregation fits well with the experimental results. Equation 16 shows again that variations of the salt concentration altering the observed values of K'_1 and K'_2 will affect both the asymmetry of the curves and the apparent affinity of hemoglobin for its ligands.

Another observation that supports the idea of changes in aggregation affecting the reactions of hemoglobin has been recently reported by Briehl (*15*). The hemoglobin of lamprey are simple chain molecules with one iron atom per chain; their oxygen dissociation curves plotted as percentage of saturation against p_{O_2} are of the hyperbolic type, namely, they do not show "interactions." However, when the concentration of this hemoglobin is increased the shape of the curves of percentage of saturation plotted against p_{O_2} becomes sigmoid indicating that a curve of log L plotted against x will be asymmetric. Simultaneously there is an increase in the sedimentation constants, which indicates aggregation. These results can be understood in terms of the box again, since Eq. 16 shows that the asymmetry appears only when the terms containing C°_{Hb} reach a certain magnitude dependent upon the values of K'_1 and K'_2. Thus, the experiments with lamprey hemoglobin indicate similar behavior to mammalian hemoglobins, except for the magnitude of the aggregation equilibrium constants and the concentration necessary to reveal the asymmetric dissociation curves.

Discussion

At this juncture let us review our conclusions. The shifting or translation of the dissociation curve with change in total hemoglobin concentration rules out the possibility of explaining the data on the basis of the Adair hypothesis alone, and concomitantly and incontestably requires that aggregation phenomena must be included in any correct representation of hemoglobin reactions. That the curve of log L plotted against x changes shape as well as translates with dilution rules out the possibility of explaining the data in terms of a single aggregation reaction. However, the known chemistry and data are consistent with the aforementioned hypothesis of box stoichiometry. Assuming the validity of our assignment of the stoichiometric coefficients, there are only three unknown constants and not four, as in the sequential reaction hypothesis, to be determined. Furthermore, unlike the Adair formulation, these three unknowns may all be independently determined by separate and direct experiments and therefore the consistency of the analysis does not depend upon curve-fitting analysis. It should be pointed out that we have not ruled out the possible necessity of including sequential steps in each of the paths of the box reaction. Nor, similarly, have we ruled out other complications such as the effect of distinguishable dimeric species on the thermodynamic analysis. The data available at present cannot answer such questions and therefore further experiments are necessary to extend this analysis quantitatively.

It should also be emphasized that the box analysis must be considered in terms of all the rate-limiting reactions contributing to the overall equilibrium. It cannot be considered as a single predominating "main" reaction such as one of the diagonal reactions in the box. The mathematical expression representing the box is only one of the several equivalent equations that may be developed to analyze the system at thermodynamic equilibrium in terms of the constraints and definitions given. This is a consequence of the fact that the Gibbs' free energy is a thermodynamic function of state and therefore independent of the path.

Similar phenomena might be anticipated for myoglobin. Preliminary inspection of the scanty data for myoglobin reactions available from the literature (*16*) shows asymmetries. Under certain conditions higher aggregation states are apparent in myoglobin solutions (*17*). Further experimental data are necessary to extend this analysis of myoglobin reactions.

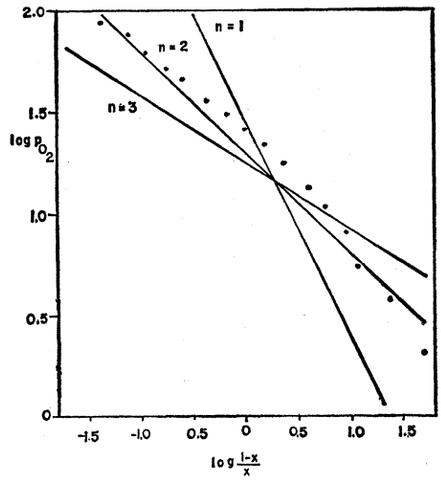

Fig. 2. Curves obtained from the data of curve A of Fig. 1. Solid lines correspond to slopes of n = 1, 2, and 3 in the Hill Eq. 6. Compare Eq. 12 for plotted variables.

The box system that is presented here to explain the reactions of hemoglobin with gaseous ligands can also explain similar phenomena that characterize other hemoglobin addition reactions, such as the asymmetries observed in the titration curves of hemoglobin with sulfhydryl-binding reagents (*18*). Another interesting effect observed in hemoglobin reactions, the pH shift or Bohr effect (*19*), can also be

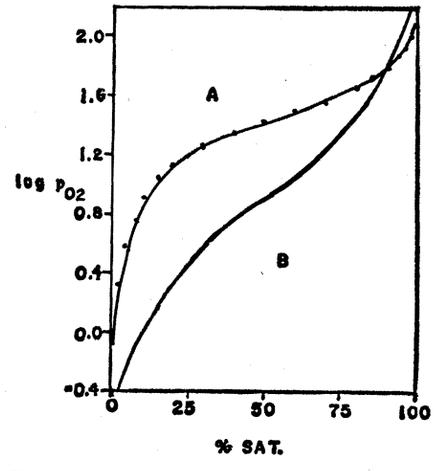

Fig. 3. Titration curve for oxygenation of hemoglobin. Curves A and B correspond identically to curves A and B, respectively, in Fig. 1. Note the asymmetry of curve A about the midpoint. Curve B is symmetric about x = 50 percent, corresponding to the rectangular hyperbola of Fig. 1.

explained by the box system. The influence of pH on the dissociation curve will vary with the dependence of K_{obs}, K'_1, and K'_2 on pH. A complete analysis would require an extension of the stoichiometric scheme by constructing additional boxes upon each one of the sides of the central box. In every one of these new boxes, the proton dissociation equilibria of each one of the species participating in the oxygen reaction would have to be considered. However, in comparing titrations at different constant pH's, in the range of pH where only the acid dissociation constants operable in K'_{obs} are involved, the curve will shift along the log-L axis without change in shape, but in regions where the acid dissociations affect the observed values of K'_1 and K'_2, the curve will also change shape and therefore its asymmetry will also be affected. In principle each of the thermodynamic constants in this analysis may be directly and independently determined experimentally, whereby the pitfalls inherent in curve-fitting procedures may be avoided. In general, any set of simultaneous reactions can be similarly analyzed.

This is a comprehensive theory dealing with all of the observed properties of hemoglobin simultaneously. The reaction paths considered, with the equations that describe them, can be applied quantitatively to the "apparent" heme-heme interaction, the Bohr effect, the Haldane effects, the heme-linked ionizations, the oxidation-reduction reactions, and the observed dissociation of hemoglobin into subunits; they are in agreement also with the observation that the structure of the reduced hemoglobin tetramer is different from the structure of the hemoglobin-ligand tetramer.

In spite of the considerable amount of work on hemoglobin reactions, a thermodynamic analysis of the data is not possible because there is no complete set of results that includes all pertinent variations of the thermodynamic constraints. Such studies are being undertaken in our laboratories in order to determine the thermodynamic parameters of hemoglobin reactions (*20*).

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News and Comment

Graduate Education: Navy Program in Rocket Astronomy Opens New Horizons to University Scientists

A Navy space research program, which dates back to the pioneer days of rocketry at the end of World War II and, in the intervening years, has won a reputation for solid accomplishment in the new field of rocket astronomy, this fall will begin to play a more active part in the education of astronomers and physicists.

Graduate students, postdoctoral fellows, and faculty members will be able to work with the staff of the atmosphere and astrophysics division of the Naval Research Laboratory (NRL) in Washington by an arrangement under which the National Science Foundation provides grants for the visiting scientists and funds for rockets, satellites, and payloads to be used in their research.

Reciprocal benefits presumably will accrue from the project; the visiting scientists should profit from association with experienced government scientists and from the opportunity to join in rocket-borne experiments, while the regular staff members should be stimulated by what division superintendent Herbert Friedman calls the "give and take" of a graduate school atmosphere.

The new scheme can be numbered among various efforts that have been made in recent years to utilize the resources and staff of specialized laboratories operated or financed by the government to increase the supply of scientific manpower in fields in which the supply is short.

The meeting ground for government and university scientists will be the E. O. Hulburt Center for Space Research, established early this year at the Naval Research Center under the joint sponsorship of the Office of Naval Research—NRL's parent organization—and NSF. The center's permanent staff is made up of researchers in Friedman's division, and some additional professionals and technicians are to be recruited specifically to work at the center.

The Navy's rocket and satellite astronomy program goes back to 1946 and the days when the United States used liberated German V-2 rockets to launch a serious program of research in space.

In the early years of the program, while American-made rockets were getting out of the pinfeathers stage,