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The IUBMB Recommendations on Symbolism and Terminology in Enzyme Kinetics

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Abstract

Recommendations on the symbolism and terminology of enzyme kinetics were approved by the International Union of Biochemistry in 1981. They were primarily necessitated by the need for a systematic treatment of reactions of more than one substrate, but some important omissions have subsequently become evident, and a decision is needed as to whether these warrant the preparation of new recommendations, and if so whether these should constitute a complete revision of the entire document, or just the preparation of some new sections.

Introduction

The explosive growth in systems biology in the early years of the 21st century has brought with it a new interest in incorporating kinetic data enzymes into models of metabolism. Enzyme databases have greatly increased in importance, but their work has been severely impeded by the lack of standards for reporting kinetic data. However, the problem is not new: even 50 years ago the newly born International Union of Biochemistry was concerned that in the absence of any guiding authority the nomenclature of enzymology was getting out of hand, and it created the Commission on Enzymes as a remedy. The *Report of the Commission on Enzymes* [1], published in 1961, was mainly concerned with the naming of enzymes, but it also included brief recommendations on the symbols and terminology of enzyme kinetics. In a later reference to these, the 1973 edition of *Enzyme Nomenclature* [2] stated that "obviously, it would be of great advantage if all authors used the same system of

symbols in their mathematical equations." Is this so obvious, however? Is it even true? In this chapter I shall examine how the perceived needs of the subject led to the current recommendations on *Symbolism and Terminology in Enzyme Kinetics* [3], and I shall discuss how well these serve the needs of biochemistry 25 years later.

As long as biochemists were concerned mainly with single-substrate reactions there was little necessity for standardized symbols and terminology. If two different papers used the symbols k_{-1} and k_2 for the same rate constant, or if the same symbol k_2 was used for two different rate constants, only minor confusion was generated. However, the development in the 1950s of serious interest in reactions of two or more substrates introduced new difficulties, because numerous symbols were needed and translation from one system to another was neither obvious nor trivial: a pair of papers would use the same symbol for one quantity, different symbols for another, and the same symbol for two different quantities. Among many examples (see below), the K_{AB} of Bloomfield, Peller and Alberty [4] was the same as K_{AB} of Alberty [5], but their K_A was Alberty's K_{AB}/K_A.

The *Report of the Commission on Enzymes* [1], published by the International Union of Biochemistry in 1961, made tentative steps towards defining consistent symbols and terminology in enzyme kinetics, but the recommendations were omitted (without any indication of the reasons) from the 1979 edition of *Enzyme Nomenclature* [6]. The problems had not disappeared, however, and in 1978 – 1979 the views of numerous biochemists interested in kinetics were solicited. Following these consultations the International Union of Biochemistry set up a panel to prepare a complete set of recommendations on *Symbolism and Terminology in Enzyme Kinetics*, and these were approved in 1981 [3]. They tried, while taking account of the existing practices in biochemistry, to bring them into closer accord with the *Report on Symbolism and Terminology in Chemical Kinetics* that IUPAC had approved in 1981 [7]. IUB claimed in 1973 that their recommendations of 1961 had been "widely followed" [2], but this assessment was more wishful thinking than fact. Subsequently, the 1981 recommendations [3] have had some influence on biochemical practice but they have by no means been overwhelmingly adopted. Moreover, some important omissions, such as the lack of treatment of reversible reactions, have become especially important with the development of interest in computer modelling of metabolism, added to the importance that they already had for studies of biochemical thermodynamics.

The International Union of Biochemistry and Molecular Biology now needs to decide whether these omissions are sufficiently important to warrant the preparation of new recommendations, and if so whether these should constitute a complete revision of the entire document, or just the addition of some new sections.

Organizations Involved in Making Recommendations

The various bodies that have been involved in making recommendations on enzymes and enzyme kinetics have experienced as many changes in name and abbreviations as most topics in biochemistry itself, and so it may be helpful to list them. The *Commission on*

Enzymes of the International Union of Biochemistry, more often called the *Enzyme Commission*, was created in 1956 and made its report in 1961 [1]. It was then replaced by the IUB *Standing Committee on Enzymes*, which had responsibility for maintaining the nomenclature of enzymes until this was transferred to the IUB *Nomenclature Committee* when this was created in 1977.

Although the Enzyme Commission ceased to exist in 1961, its disappearance went unnoticed by most biochemists and references to it are still made today. Its name survives in the prefix EC used for enzyme numbers in *Enzyme Nomenclature* [8]. Despite the obvious advantages of EC numbers, their use in publications was patchy for many years, as by no means all of the major journals of biochemistry insisted on it. However, the greatly increased importance of computer databases in recent years has brought with it enhanced awareness of the need to identify enzymes unambiguously, and there is now much wider recognition that EC numbers provide the best chance currently available of achieving this. Nonetheless, the thoroughly objectionable practice of referring to enzymes simply as gene products, calling nitrate reductase the product of the *nar* genes, for example, remains common. It is hard to think of any legitimate reason to do this, not only implying that enzymes exist only to express what is recorded in the genome, but also utterly obscure to all but the small circles of researchers who work with the enzymes in question.

The IUBMB has always worked in conjunction with IUPAC in matters of biochemical nomenclature, and until 1977 most aspects of this were in the hands of the IUPAC-IUB Commission on Biochemical Nomenclature. This was reconstituted in 1977 as the IUPAC-IUB Joint Commission on Biochemical Nomenclature, the IUB Nomenclature Committee being created at the same time to deal with topics that IUPAC did not wish to handle (most notably enzyme nomenclature). In practice these two committees have always held joint meetings, with a common Chairman and Secretary. It may be noted that just as biochemists continue to refer to the Enzyme Commission as a living entity more than 40 years after it ceased to exist, they also frequently attribute to IUPAC recommendations that were actually made jointly by IUPAC and IUBMB, or even, like most of recommendations about enzymes, by IUBMB alone.

For about 20 years the International Union of Biochemistry also promoted a Committee of Editors of Biochemical Journals, which had responsibility for maintaining liaison with the nomenclature committees and ensuring that the recommendations made were consistent with current practice.

The names and abbreviations of the various organizations are listed in Table 1. As several of the names are cumbersome and unmemorable they are replaced in the remainder of this article by the abbreviations given in the right-hand column.

Constituton of the IUB Panel of 1981

The panel set up by IUB consisted of seven members, A. Cornish-Bowden, H. B. F. Dixon, K. J. Laidler, J. Ricard, I. H. Segel, S. F. Velick and E. C. Webb, and numerous other biochemists were also consulted. The convener was initially Segel, but he subsequently resigned and was replaced by Cornish-Bowden. Laidler had recently prepared a report for IUPAC on *Symbolism and Terminology in Chemical Kinetics* [7], and the first draft of the IUB recommendations [3] was in fact written by him.

Basic Definitions

The first part of the 1981 document [3] defined various terms of importance in enzyme kinetics, such as *catalysis*, *enzyme*, *substrate* etc. As these excite little controversy they will not be discussed here. One topic that did generate some disagreement, however, was the labelling of generic substrates, products and inhibitors. As long as there was only one of each the traditional use of S for substrate, P for product, and I for inhibitor created no difficulties, but these started to appear with studies of reactions with two or more substrates. Simply adding subscripts, as in S_1, S_2, etc., creates no logical difficulty, but it does add to the typographical complications of a subject already overburdened with subscripts, superscripts, primes etc., and most authors have preferred an alphabetical system with substrates A, B, etc., products P, Q, etc., and inhibitors I, J, etc. The 1981 recommendations used such a system for illustration, apart from using Z, Y etc. for products, as in the well known textbook of Laidler and Bunting [9], rather than P, Q, etc.; however, they emphasized that the essential point is not to try to impose a uniform system for use in all circumstances, but to expect authors to define the symbols they use and to use them consistently.

Table 1

Full name	Period	Abbreviation
International Union of Biochemistry	1955 – 1991	IUB
International Union of Biochemistry and Molecular Biology	1991-present	IUBMB
International Union of Pure and Applied Chemistry	1919-present	IUPAC
IUB Commission on Enzymes	1955 – 1961	EC
IUB Standing Committee on Enzymes	1961 – 1977	(none)
IUPAC-IUB Commission on Biochemical Nomenclature Nomenclature	Until 1977	CBN
IUPAC-IUB Joint Commission on Biochemical Nomenclature	1977 – 1991	JCBN
IUPAC-IUBMB Joint Commission on Biochemical Nomenclature	1991-present	JCBN
IUB Nomenclature Committee	1977 – 1995	NC-IUB
IUBMB Nomenclature Committee	1995-present	NC-IUBMB
IUB Committee of Editors of Biochemical Journals Journals	1955 – 1990	CEBJ

Order of Reaction and Rate Constants

The recommendations on order of reaction likewise produced little disagreement, but this section also dealt with the numbering of rate constants, a topic that had excited extensive discussion among biochemists; indeed, it accounted for about 40% of the total length of the chapter on Symbols of Enzyme Kinetics in the *Report of the Commission on Enzymes* [1]. The essential disagreement was between those who preferred the practice common in chemistry of referring to the forward and reverse rate constants for the first reaction in a sequence as k_1 and k_{-1}, and those who followed what had been long-standing practice in biochemistry of calling them k_1 and k_2 respectively. The Enzyme Commission preferred the former system, but felt that the existence of k_2 in both systems but with different meanings when applied to a simple two-step Michaelis-Menten mechanism was a source of ambiguity, and they proposed prefixing the positive subscripts with + signs, replacing, for example, k_1 by k_{+1}.

This matter had by no means been resolved to general satisfaction in 1981, but the Panel at that time felt that the emphasis in previous discussions had been misplaced. Rather than seeking to impose a universal system that could be used without definition, the essential was for authors to define whatever symbols were most appropriate for their purposes. Within the document itself the first of the systems mentioned was used for illustration, the + signs being treated as unnecessary.

Since 1981 the use of even-numbered indices for reverse reactions has not disappeared from the literature, but it seems to be in the process of doing so. Of 21st century textbooks, only one [10][1] still follows this system; all others known to me [11 – 14] use negative indices. Although the numbers involved are too small to be statistically significant, this is quite different from the case in 1981: at that time, only one [15] of the textbooks known to me followed what were then the recommendations and included + signs, five used negative indices but did not write + signs with positive indices [9, 16 – 19], and five avoided negative indices by using even-numbered indices for reverse steps [20 – 24].

Reactions Involving More Than One Substrate

The discussion of simple Michaelis-Menten kinetics requires no comment here, but matters became more complicated with the consideration of reactions of two or more substrates. In the earliest discussion of two-substrate kinetics known to me, Haldane [31] used numbered binding constants accompanied by the symbols x and y for the two concentrations:

$$\frac{V}{v} = 1 + \frac{K_4}{x} + \frac{K_3}{y} + \frac{K_1 K_2}{xy} \qquad (1)$$

[1] Although Leskovac [10] incorporated a substantial amount of material from the 2nd edition of my book [14], he did not number the rate constants in the same way.

The subsequent development of the subject by Alberty and others in the 1950 s led to wide variation in symbols: the K_{AB} of Alberty [5] was the same as that of Bloomfield *et al*. [4], but was written as $K_{ia}K_b$ by Cleland [25]; on the other hand, Alberty's K_A was the same as Cleland's K_a, but different from the K_A of Bloomfield *et al*., despite the fact that Alberty was an author of two of these papers [4, 5]. Even with just three systems to compare there was ample scope for confusion, but in fact by the middle 1960s at least five or six different systems were in widespread use. Of these, the one introduced by Dalziel [26] was quite different from the others: less likely, therefore, to invite ambiguity, but also less easy to be understood by readers unfamiliar with it. It is now rarely used, but in 1981 it was still sufficiently frequent for the IUB Panel to think it worthwhile to include a note on the pronunciation of "Dalziel" (virtually identical to that of the prefix in DL-lactic acid).[2]

In this confusing environment Mahler and Cordes [27] noted the variation in symbols used by different authors in the 1950s and 1960s. As their emphasis was on the symbols used rather than on the way of organizing them into a rate expression, all of the rate equations were written in the same way, as expressions for the reciprocal rate, though they were not all written in this way in the original publications; the same convention is followed here. Alberty [5] wrote:

$$\frac{V_f}{v_f} = 1 + \frac{K_A}{A} + \frac{K_B}{B} + \frac{K_{AB}}{AB} \tag{2}$$

though in another paper [4] he used a different system:

$$\frac{V_{AB}}{v_f} = 1 + \frac{K_{AB}}{K_B}\frac{1}{A} + \frac{K_{AB}}{K_A}\frac{1}{B} + \frac{K_{AB}}{AB} \tag{3}$$

whereas Dalziel [26] wrote:

$$\frac{e}{v_f} = \phi_0 + \frac{\phi_1}{S_1} + \frac{\phi_2}{S_2} + \frac{\phi_{12}}{S_1 S_2} \tag{4}$$

and Cleland [25] wrote:

$$\frac{V_1}{v_1} = 1 + \frac{K_a}{A} + \frac{K_b}{B} + \frac{K_{ia}K_b}{AB} \tag{5}$$

[2] The need for this note was suggested by the fact that the Russian translator of my first book [32] used a footnote to mention that some Soviet authors wrote the name as Dal'tsil, implying that that was incorrect. The translator himself wrote the equivalent of Diil, which was also incorrect.

Despite their concern for this variation, Mahler and Cordes [27] used none of the systems then in use, but introduced a new one of their own:

$$\frac{V_1}{v_1} = 1 + \frac{K_a}{a} + \frac{K_b}{b} + \frac{\bar{K}_a K_b}{ab} \tag{6}$$

Their symbols have subsequently been adopted by essentially no other authors, in part because of the difficulty of printing symbols with overbars, but also because the use of overbars for distinguishing between Michaelis constant and inhibition constants is not obvious at sight but needs to be learned. Rather surprisingly, they did not list the symbols used in the textbook by Dixon and Webb [28, 29], though this was very widely used at the time they were writing:

$$\frac{ke}{v} = 1 + \frac{K'_a}{a} + \frac{K'_b}{b} + \frac{K_a K'_b}{ab} \tag{7}$$

They did, however, refer mysteriously to symbols used by the "Enzyme Commission", symbols that occur nowhere in the *Report of the Commission on Enzymes* [1]. They are identical to those used *later* by Dixon and Webb [30], though not in the editions of their book [28, 29] that would have been available to Mahler and Cordes while they were writing:

$$\frac{V}{v} = 1 + \frac{K_m^A}{a} + \frac{K_m^B}{b} + \frac{K_s^A K_m^B}{ab} \tag{8}$$

One may surmise that they learned of these symbols from correspondence with Dixon, who had been, as noted previously, the Chairman of the original Commission on Enzymes. As may be deduced from the forms of the equations, Dalziel [26] designated the substrates as S_1 and S_2, but they were designated as A and B by all of the other authors mentioned, including Haldane [31], who, however, wrote their concentrations as *x* and *y* respectively.

Consistent with their attitude to other questions of uniformity, the members of the IUB Panel of 1981 considered that the essential point was not to try to impose a universal system, but to insist on the necessity to define whatever symbols authors choose to use.

For illustrative purposes they used symbols very similar to those of Dixon and Webb [30], but with the substrate indicated by a second subscript rather than by a superscript:

$$\frac{V}{v} = 1 + \frac{K_{\mathrm{mA}}}{a} + \frac{K_{\mathrm{mB}}}{b} + \frac{K_{\mathrm{iA}} K_{\mathrm{mB}}}{ab} \tag{9}$$

They also moved (silently) from italic to roman subscripts, replacing K_{mA} with K_{mA}, and so on. No reason was given for the change, but it agrees with present IUPAC recommendations [33]. It may be explained by the fact that *K* is here an algebraic variable, and should follow the normal mathematical convention of representing such variables by italic sym-

bols. The subscripts, however, are not algebraic variables and should not be printed as if they were. In particular, m is not an index but the first letter of the name Michaelis, and A represents a chemical species, and should not therefore be written in italics either.

Most of the systems listed in these equations fail to distinguish between symbols for chemical species and symbols for their concentrations, even though these are logically distinct: the identity of a chemical species is not the same as its concentration. For example Alberty [5] used *A* both for the first substrate and for its concentration. Most of the early authors made no distinction, but for Dixon and Webb [28] *a* was the concentration of A, and so on. Some authors, such as Laidler and Bunting [9], preferred to use square brackets for concentrations, [A] for the concentration of A, for example.

The recommendations of IUB [3] considered the distinction important, and indicated that square brackets could be used without definition, but recognized that other systems might sometimes be typographically more convenient and were unobjectionable if defined in context. In the discussions within the Panel, some members thought that italic and roman type alone were sufficient to make the distinction (with *A* as the concentration of A), but the majority view was that differences between italic and roman type pass unnoticed by many readers and were thus inadequate to make an important conceptual distinction. *An extended piece of text in italics is, of course, quite obvious*, but an isolated letter *A* is much less obviously different from an isolated roman A. In any case, there are wide variations in what different people consider to be obvious, most simple truths being obvious once they have been pointed out.[3]

Inhibition

The treatment of enzyme in the 1981 document [3] is relatively brief, being mainly directed towards the classification of inhibition types as *reversible* or *irreversible*, as *linear* or *non-linear*, and as *competitive*, *uncompetitive*, *mixed* or *non-competitive*. In view of the great and growing importance of enzyme inhibition in drug development [37], a case could doubtless be made that a more extended treatment is now needed, and this is a question that NC-IUBMB should examine.

The names *competitive* and *uncompetitive* for the two extreme cases of linear inhibition (with effects on the apparent values of the specificity and catalytic constants respectively) are now widely accepted, and there was no support among the members of the Panel for the term *anticompetitive* used, for example, by Laidler and Bunting [9] in their textbook. The major disagreement that existed in 1981 and has still not been resolved is the name that

[3] The current scandal [34] over faked data in the *New England Journal of Medicine* illustrates this well. The same micrograph was used to illustrate results supposedly obtained with two different patients [35], and the similarity between the two panels of the relevant figure is so obvious that one might think it could hardly fail to be noticed even with an inexpert eye. Nonetheless, in reality it did pass unnoticed for several years, not only by the referees and editors, but also by readers of the article; it only came to light after revelation that fraudulent data from the same group had been published in another journal [36].

should be given to the range of intermediate cases in which there are effects on the apparent values of both the specificity and the catalytic constants, and the name, if any, to be given to the special case of this in which the effects on the two constants are equal. Although there was general agreement with Cleland's view that this special case had no particular mechanistic or other importance [38], and therefore had no need for a unique name, there was much less agreement with his view that the name *non-competitive* that had been given to this case for many years could therefore be generalized to encompass the whole intermediate range. The problem with this loosening of the definition is that the restricted meaning was still very widely used, and continues to be, and the shorter term *mixed* (or *mixed-type*) was already available for the general case. The Panel therefore preferred to follow the usage of Dixon and Webb [30], in which *non-competitive* refers to the special case, and *mixed* to the general case.

Nonetheless, the view that the usage of Dixon and Webb is unambiguous has not met with universal agreement. Copeland [37], for example, recently commented as follows: "In my experience, the term mixed-type inhibition can lead to misunderstandings about the physical meaning of the term (e. g., I have had discussions with chemists who have mistakenly believed that mixed-type inhibition must require two inhibitor molecules binding to separate sites on the enzyme); therefore we will use the term non-competitive inhibition in its broader definition to describe any inhibitor that displays affinity for both the free enzyme and the ES complex." However, this argument appears unconvincing.[4]

Although there has long been agreement that linear inhibition is characterized by two different inhibition constants (for the competitive and uncompetitive components, either of which may be negligible), there has been less agreement about how they should be symbolized. When only one constant is relevant it is normally symbolized K_i, but when both are needed Dixon and Webb [30], for example, used K_i for the competitive inhibition constant and K'_i for the uncompetitive inhibition constant, whereas Cleland [38] used K_{is} and K_{ii} respectively (for $K_{i\,slope}$ and $K_{i\,intercept}$ respectively, referring to the slope and ordinate intercept of a plot of reciprocal rate against reciprocal substrate concentration).

In the 1981 recommendations [3] both of these conventions were considered unsatisfactory, the use of primes being unsystematic and the second subscripts *s* and *i* being derived from a particular type of plot with no necessary relationship to the subject. (With plots of substrate concentration divided by rate against substrate concentration, for example, Cleland's K_{is} refers to the ordinate intercept and K_{ii} to the slope, an inversion of roles that can hardly fail to be confusing.) For these reasons the symbols K_{ic} and K_{iu} were recommended for the competitive and uncompetitive components respectively. Although not yet in universal use, these have been widely adopted.

[4] I have encountered biochemists who feel strongly that MoCo is a clear and satisfactory abbreviation for "molybdenum cofactor", but I doubt whether many chemists would find that a convincing reason to abandon Co as a symbol for cobalt.

Activation

Activation was also dealt with rather briefly in the 1981 recommendations, but two points of nomenclature needed to be addressed. First, it was noted that although classification of activation as linear or non-linear often has the same results as classifying it as *essential* or *non-essential*, exceptions are possible, because in principle essential activation (in which the enzyme has no activity in the absence of activator) can be non-linear (so that the reciprocal rate is not a linear function of the reciprocal concentration of activator).

A more important point was to emphasize that although the different kinds of linear activation are analogous to the familiar classes of inhibition, the name *competitive* cannot be used for the type of activation in which the activator binds only to the free enzyme because there is nothing that can be considered a competition in such a mechanism. Although less obviously objectionable, the terms *uncompetitive* and *non-competitive* were also recommended to be avoided for describing activation. Instead, the names *specific activation* and *catalytic activation* (corresponding to competitive and uncompetitive inhibition respectively) were suggested for effects on the apparent values of the specificity constant and catalytic constant respectively, *mixed activation* being entirely acceptable for the case where both effects are present.

Although the recommendations did not mention it – doubtless wanting to avoid the storm of protest that would have greeted any suggestion of abandoning the term *competitive* altogether – the terms *specific* and *catalytic* could perfectly well be applied to inhibition as well, resulting in an exact correspondence between the terms used in activation and inhibition. However, biochemists in general have been far more interested in inhibition than in activation, and would certainly resist any change to inhibition terminology that was introduced solely with the aim of greater concordance with activation terminology. Nonetheless, in contexts where both activation and inhibition need to be discussed together it is simplest to qualify both as *specific*, *catalytic* or *mixed* [see, e. g., 39].

pH Effects

The discussion of pH dependence in the recommendations of 1981 [3] introduced no new principles or terminology, and was in general based on what was already common practice in the literature. It requires no discussion here.

Pre-Steady-State Kinetics

The discussion of pre-steady-state kinetics in the recommendations of 1981 [3] was rather brief, in part because there was no particular need in enzyme kinetics to depart from normal practice in chemistry, and so the IUPAC recommendations [7] should cover most needs,

and in part because the members of the panel were mainly people with experience of steady-state kinetics: preparation of recommendations for pre-steady-state kinetics would require a different panel.

One point that such a panel might wish to consider was brought to my attention by Gösta Pettersson during preparation of the current edition of my textbook [14]: equations for pre-steady-state kinetics typically contain terms of the form $A\exp(-\lambda t)$, where A is a constant known as the *amplitude*, t is the time and λ is a constant with dimensions of reciprocal time: it is the reciprocal of a time commonly symbolized as τ and called the *relaxation time* or the *time constant*, but λ has no generally accepted name of its own. Although it has the dimensions of a first-order rate constant, it is not in general the rate constant of any particular first-order reaction, so terms such as "apparent first-order rate constant" are not only cumbersome but also potentially misleading. Pettersson proposed the name *frequency constant* for λ. Authoritative texts [e. g. 40, 41] typically switch arbitrarily between writing equations in terms of λ and in terms of τ, and often write $1/\tau$ rather than λ. In a well known textbook [42] a table entitled "Physical meaning of the relaxation time, τ" actually tabulates not τ but $1/\tau$.

Reversible Reactions

As noted already, the 1981 recommendations [3] paid very little attention to the reversibility of enzyme-catalysed reactions. However, even in the simplest case of a one-substrate one-product reaction there are points to be taken into account, most obviously that the rate equation cannot be linearized by writing it as an expression for reciprocal rate and that therefore there is no advantage in taking reciprocals at all; some such form as:

$$v = \frac{V^{\mathrm{f}}a - \frac{V^{\mathrm{r}}K_{\mathrm{mA}}}{K_{\mathrm{mP}}}p}{K_{\mathrm{mA}}(1 + p/K_{\mathrm{mP}}) + a} \tag{10}$$

is as simple as one can obtain. The concentrations and Michaelis constants can be represented in the same way as in the irreversible case, but some additional convention is needed to distinguish between the forward and reverse limiting rates, and superscript f and r respectively are used in this example.

Nonetheless, representing the equation like this has some disadvantages, which become more important when one needs to consider more complicated examples, such as equations for reactions with multiple substrates and reactions that do not obey Michaelis-Menten kinetics. Equation 10 obscures at least two points: it fails to illustrate the symmetry of the behaviour with respect to substrate and product, and it fails to separate it into the components – catalytic activity of the enzyme, thermodynamic state of the reaction, degree of saturation of the enzyme – that characterize any enzyme-catalysed reaction. This separation becomes much clearer if we rearrange it into the following form, where K is the equilibrium constant:

$$v = \frac{\frac{V^{\mathrm{f}} a}{K_{\mathrm{mA}}}\left(1 - \frac{p/a}{K}\right)}{1 + \frac{a}{K_{\mathrm{mA}}} + \frac{p}{K_{\mathrm{mP}}}} \tag{11}$$

Here the right-hand factor in the numerator separates the thermodynamic state of the reaction from any properties that the enzyme may have. In particular, as the only term in the equation that can be negative it is the only term that decides the direction in which the reaction will proceed, but as it contains no kinetic information it says nothing about how fast it will do so. When the equation is written in this way the thermodynamic factor is fixed, regardless of mechanistic complexities, but the rest of the equation can be freely modified (as long as no negative quantities are introduced) without violating any thermodynamic constraints.

Non-Michaelis-Menten Kinetics

The section of the recommendations of 1981 [3] in most obvious need of revision is that dealing with reactions that do not obey Michaelis-Menten kinetics. This was partly because discussions of this topic are normally focused on mechanisms and models of cooperativity [e. g. 43 – 45], which were inappropriate topics for extensive discussion in a nomenclature document, and partly because the need for reasonably simple rate equations that could be used in metabolic models for fully reversible reactions [46] was not apparent at that time. For irreversible cases the Hill equation was already widely used as a simple alternative to mechanistically realistic equations that are too complicated to use, and the recommendations made several important points about it. As long as the thermodynamic factor in the reversible case is written as in Equation 11 the equation will remain thermodynamically correct; this important point has not always been realized in discussions of cooperative kinetics in the literature, and equations have sometimes appeared that suggest that non-thermodynamic factors may determine the direction of a reaction.

The Hill equation can be regarded as a variant of the Michaelis-Menten equation in which both the substrate concentration and the half-saturation concentration (not the Michaelis constant: see below) are raised to a power h known as the *Hill coefficient*. In the literature the Hill coefficient had often been written as n, a symbol that invited confusion with the number of binding sites for substrate on the enzyme, or as n_{H} by authors who were aware of the danger of confusion and wished to avoid it; the alternative h, which has become the recommended symbol, was already occasionally found in the literature though it was unusual. The symbol n was definitely discouraged, on account of the danger of confusion noted; n_{H} was not discouraged, but it was noted that it was typographically inconvenient to include a subscript in a symbol that represents an exponent and therefore sometimes needs to be printed as a superscript to a symbol that already has a subscript: $\mathrm{K}^{n\mathrm{H}}{}_{0.5}$, for example, is legible if carefully printed, but less legible than $\mathrm{K}^{h}{}_{0.5}$.

There is one other major point that was noted in the recommendations of 1981 [3], albeit in an unfortunate context (section 4.3 rather than the more appropriate section 11): the Michaelis constant K_m is by definition a parameter of the Michaelis-Menten equation, and has no meaning for non-Michaelis-Menten kinetics. Failure to appreciate this remains commonplace in the literature. To avoid the error one needs to replace any symbol like K_{mA} with a generic symbol like $a_{0.5}$ that suggests half-saturation without implying any particular kinetic equation.

Taking account of these considerations, a form of the reversible Hill equation that avoids violating thermodynamic constraints would be as follows (as suggested in [46]):

$$v = \frac{\frac{V^f a}{a_{0.5}}\left(1 - \frac{p/a}{K}\right)\left(\frac{a}{a_{0.5}} + \frac{p}{p_{0.5}}\right)^{h-1}}{1 + \left(\frac{a}{a_{0.5}} + \frac{p}{p_{0.5}}\right)^{h}} \qquad (12)$$

Notice that this simplifies to Equation 11 when $h = 1$.

Transport Processes, Insoluble Enzymes, etc.

There are several topics that are completely missing from the recommendations of 1981. Although it is widely recognized that the kinetics of transport processes have much in common with the kinetics of enzyme-catalysed reactions, and transporters are quite similar to enzymes, there appears to have no attempt to harmonize terminology in these closely related subjects. Indeed, at the time of writing the IUBMB have not approved any recommendations at all in the area of transport processes. Similarly, even if they do not state it explicitly the 1981 recommendations mainly assume that they are dealing with enzymes in free aqueous solution, and contain no mention, for example, of processes that take place at lipid-water interfaces. In the future the IUBMB will need to consider whether these topics should be dealt with separately, or incorporated into new recommendations about enzyme kinetics.

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