

## Erratum

### Requiem for the reaction-rate equation?\*

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Received 25 April 2002; accepted 11 June 2002

#### 1. Introduction

In a *Perspectives in Catalysis* article that appeared recently in *Catalysis Letters*, Professor Michel Boudart hailed a coming revolution in catalytic kinetics [1]. He predicts that the twenty-first century will be dominated by the **rate constant**, which will be determined by a combination of microkinetic analysis, computational chemistry, and surface science techniques. By contrast, the twentieth century belonged to the **rate equation**, elucidated using a mechanistic approach to kinetic modeling and supported by discrete experimental data sets arising from a large number of reactions carried out over a range of reaction conditions. Boudart argues that by perfecting the methodology of microkinetic analysis over the next few decades, kinetics-assisted design of catalysts will become predictive, obviating the need for rate equations.

Since catalysis is a kinetic phenomenon [2], an approach advocating a prominent role for kinetics in the future development of protocols for discovery, design, and rapid screening of catalysts holds great promise. However, it is perhaps premature to hold a requiem for the rate equation in catalytic reaction kinetics. Indeed, I would argue that the role of the rate equation is currently in *ascendance* in one area of growing importance, that of research involving the complex organic catalytic reactions common to pharmaceutical applications. In this field, kinetic analysis and the determination of rate constants *via* the rate equation presents exciting opportunities for future research, aimed at increasing fundamental mechanistic understanding, aiding future catalyst design, and streamlining pharmaceutical process research and development in an ever more competitive environment.

The key to this “back-to-the-future” approach to reaction kinetics in liquid-phase organic reactions lies in the recent development of accurate *in situ* experimental methods for the continuous monitoring of reaction rate as a function of reaction progress. These tools now insure that the fastest way to obtain information about these reactions is simply to run them—and by that I mean to run them just as one would in the commercial application, without resorting to experiments that measure initial rates using distorted reactant concentrations. Monitoring reactions using such *in situ* methods, we may obtain the equivalent of thousands of separate “initial-rate” measurements at different reactant concentrations in one reaction—typically over the course of an hour or less. What would Langmuir, Rideal, or Michaelis and Menten have given for access to such plentiful data for use in their rate equations?

The attraction in pharmaceuticals of an approach based on the rate equation may be stronger than in petrochemical applications. The reasons for this become more clear when we compare key characteristics of typical pharmaceutical reactions with those of the petrochemical or basic chemicals industry, where the methodology of microkinetic analysis [3] described by Boudart has been most successfully applied (table 1). Petrochemical reactions are conventionally carried out at relatively high temperatures over fixed beds of heterogeneous catalysts that maintain a constant level of conversion of the flowing gaseous reactants. The reactants are small molecules, and the products may be many. Networks describing the global reactions can be extremely complex, with parallel and consecutive elementary steps often numbering in the dozens. Incorporating all of these into an explicit rate equation may prove to be intractable. The aim of the microkinetic treatment is to identify the uni- or bimolecular rate constants for all of these steps, culminating in the presentation of a mechanism-based macroscopic picture of the reaction. For such an approach to be successful, the assembling of the data required entails extensive experimental work, including various *ex situ* adsorption and surface chemistry experiments in addition to the

\*The publisher regrets that this article first published in Vol. 83, Nos. 3–4 November 2002, pp. 133–136, appeared without any of the equations. Since the author originally supplied the complete article, the publisher accepts full responsibility for this grievous error. This version of the article, now published correctly and in its entirety, is the true representation of the author's intent. Please contact the author directly regarding reprints.

Table 1

Comparison of key features of catalytic processes in basic chemical and petrochemical applications with those in fine chemicals and pharmaceuticals

| Feature                                  | Basic chemicals or petrochemical application | Pharmaceutical or fine chemicals application |
|------------------------------------------|----------------------------------------------|----------------------------------------------|
| Type of catalyst                         | Heterogeneous                                | Homogeneous or heterogeneous                 |
| Reaction conditions                      | Relatively high temperatures and pressures   | Relatively low temperatures and pressures    |
| Type of reactor                          | Flow reactor (fixed bed, fluidized bed)      | Batch or semibatch reactor                   |
| Phase of reactants and products          | Gas phase                                    | Liquid and gas phase                         |
| Size of molecules reacted and produced   | Small                                        | Large                                        |
| Number of elementary reactions occurring | Large                                        | Small                                        |
| Catalyst turnovers required              | Many                                         | Few                                          |
| Lifetime of process                      | Long                                         | Short                                        |
| Catalyst cost                            | Low                                          | High                                         |
| Product value                            | Low                                          | High                                         |
| Product volume                           | High                                         | Low                                          |

study of the reactions themselves. Molecular modeling also plays a role in obtaining salient information for determining rate and equilibrium constants. The catalyst designed by such an approach will be used in a process that will continue to produce the same products far into the future. This allows plenty of time to think about a catalyst design or modification that may shave a fraction of a percent off costs or increase yield by a minute amount, which translates to huge economic benefits because of the sheer volume of production and longevity of the product line.

We may contrast this description with that of a typical catalytic reaction found in a pharmaceutical application. Reactions are carried out under mild conditions of relatively low temperatures and pressures, with reactants and products in the liquid phase in a stirred batch reactor. Homogeneous catalysts are used as often as heterogeneous catalysts. The organic molecules undergoing the reaction are large and complex. Although the reaction network may involve several parallel and consecutive steps, side reactions and by-products are usually minimized by the use of mild conditions and by appropriate choice of catalysts. Indeed, high chemo-, regio-, or enantioselectivity is a common feature of these reactions. Many of the elementary steps are reversible and may remain in equilibrium over the course of the reaction. Because the reaction is carried out in batch mode, the conversion level of the reactants changes continuously over time. The total production volume is several orders of magnitude lower than that typical of petrochemical applications but several orders of magnitude higher in value. Catalyst recycling is not a top priority—most often the catalyst employed in this reaction will necessarily be replaced with each batch of product because of regulatory constraints. Regulatory issues also dictate that the possibility of catalyst modification after the process goes commercial will be severely limited. Further, the entire process itself will give way in just a

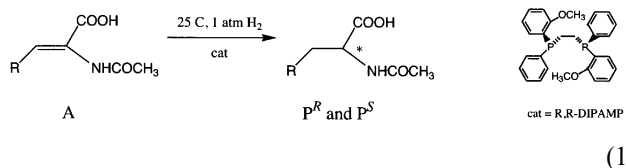
few years to that of a new reaction with new molecules possessing a different array of functional groups, possibly requiring a completely different catalyst. Since the clock on patent protection of the high-value product may already be ticking when catalyst design begins, development time has to be balanced against the drive to get the relatively short-lived process onstream as quickly as possible.

What a chemist working in pharmaceutical process research needs, therefore, is a rapid way to assess catalyst performance under the very conditions under which the reaction will be carried out in the commercial process. The rate equation is tailor-made for this. The dynamic concentration profile of reactions carried out under batch conditions is precisely what gives the rate equation its importance in these organic catalytic reactions. The kinetic behavior of catalytic reactions of this type has been compared to that of a chameleon [4], changing its colors over the course of the reaction: characteristics of a reaction will depend on the conditions under which we observe it. It is possible and even likely that a batch reaction may commence under one set of limiting conditions and pass through to another limit over the course of a single experiment. Thus an analytical rate equation, which describes the dynamic relationship between rate and concentration, is particularly well suited to help us make sense—and make use—of what we observe. Development of a mechanistic-based rate equation, coupled with kinetic modeling using the plentiful, accurate data now easily obtainable from *in situ* experimental methods, allows us to extract kinetic parameters from relatively few experiments. Other methods for obtaining these parameters for liquid-phase organic reactions are more time consuming and can be less certain. The tools of microkinetic analysis ancillary to the reaction itself include *ex situ* experimental measurements of catalyst structure, spectroscopic studies aimed at observing catalytic intermediates, adsorption or binding measurements in the

absence of solvent, and computational methods that usually describe binding and catalysis as processes occurring in a vacuum. However, these methods seldom give an accurate description of the interactions occurring within the operating catalytic cycle in the condensed phase systems that characterize organic reactions.

A key point here is a subtle shift in the spotlight, away from the *catalyst* towards the *catalysis* of the reaction itself—as a means of teaching us about how the catalyst works. We aim to learn about the reaction pathways without developing a portfolio of the catalyst's *ex situ* characteristics, or without necessarily requiring a direct observation of the catalytic species in solution; instead, we focus on following the fruits of its labor. Although it is tempting to want to “see” what the catalytic intermediates look like, important examples have shown us that the observation of a species is not a guarantee of its viability in a catalytic cycle, and indeed in numerous cases this has led us in exactly the wrong direction.

One of the most graphic illustrations of the pitfalls of a “seeing-is-believing” approach is provided by an early example in asymmetric catalysis. This story also shows how a reaction-rate equation may be used to guide us in understanding a seemingly inexplicable result. The hydrogenation of enamides using cationic Rh complexes with chiral phosphine ligands (equation (1)) became the first major commercial asymmetric catalytic process in Monsanto's production of *L*-Dopa against Parkinson's disease in the 1970s [5]. Knowles' seminal work in discovery and application of these ligands won him a share of the Nobel Prize for asymmetric catalysis in 2001. Landis and Halpern investigated this reaction in meticulous detail [6]. Their landmark work reversed the original mechanistic conclusions of the Monsanto workers and challenged the conventional paradigms we bring with us from what we know about enzymes.



The simple catalytic cycle shown in scheme 1 describes the kinetically important steps in this reaction. Spectroscopic investigations showed that the intermediate species  $[A^{*R}]$  was present in ten times higher concentration than the intermediate  $[A^{*S}]$ . However, kinetic studies ultimately revealed that hydrogenation of the minor species  $[A^{*S}]$  proceeded nearly 600 times faster than that of the major species  $[A^{*R}]$ , yielding an enantioselectivity of 98% towards the *S*-product! Product enantioselectivity was dictated not by the difference in concentrations of two intermediate species but by their relative reactivities. Thus, the standard “lock-and-key” paradigm was replaced in this case by a “major-

product/minor-intermediate” paradigm, which tells us that the lowest energy transition state cannot necessarily be predicted from the knowledge of the relative stabilities of intermediate species [7].

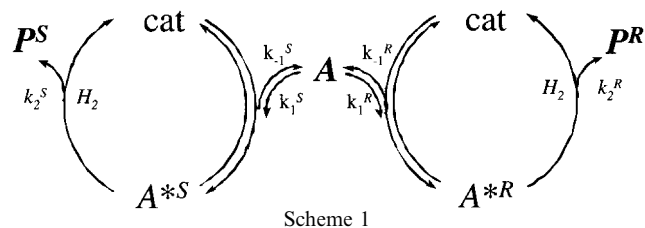
$$r_{\text{total}} = \left( \frac{k_2^R k_1^R}{k_{-1}^R + k_2^R [H_2]} + \frac{k_2^S k_1^S}{k_{-1}^S + k_2^S [H_2]} \right) \frac{[A][H_2][*]_{\text{total}}}{1 + \frac{k_1^R [A]}{k_{-1}^R + k_2^R [H_2]} + \frac{k_1^S [A]}{k_{-1}^S + k_2^S [H_2]}}$$

relative values of the  $k_2$  constants  
tells the relative reactivities of the  
*R* and *S* intermediate species

the relative values of the *R* and *S* terms  
give the relative populations of the two  
intermediate species

(2)

Landis and Halpern developed the rate equation shown in equation (2) on the basis of the steady-state treatment of the catalytic cycle in scheme 1. The rate



equation deconvolutes the contributions to the ultimate enantioselectivity derived from the relative concentrations and from the relative reactivities of the two intermediate species. Thus, the rate equation allows us to extract both kinetic and thermodynamic information from the reaction-rate data. In addition, this equation helps rationalize the observed effects of hydrogen pressure on enantioselectivity. The relationship between ee, hydrogen concentration, and the various rate constants in scheme 1 is determined from the rate equation and is given by equation (3). A lucid discussion of this pressure effect in terms of “kinetic coupling” between the binding step ( $k_1$ ,  $k_{-1}$ ) and the subsequent hydrogenation step ( $k_2[H_2]$ ) was given by Professor Boudart in this journal several years ago [8] and has been discussed in other contexts since [9].

The highlighted terms describe the rates at which the intermediate species are poised to react....

$$\frac{\text{rate}^R}{\text{rate}^S} = \frac{1+ee}{1-ee} = \frac{k_2^R k_1^R}{k_2^S k_1^S} \frac{k_{-1}^S + k_2^S [H_2]}{k_{-1}^R + k_2^R [H_2]}$$

(3)

But do we really need a rate equation to take all this in? It is true that all of the conclusions discussed above for this catalytic system could have been reached, and

Table 2

Values of the rate constants in scheme 1 for reactions carried out at 298 K, 1 at H<sub>2</sub>, as reported by Landis and Halpern in reference [6]

| Rate constant                            | R-pathway                     | S-pathway                      |
|------------------------------------------|-------------------------------|--------------------------------|
| $k_1$ (M <sup>-1</sup> s <sup>-1</sup> ) | $1.06 (\pm 0.06) \times 10^4$ | $5.30 (\pm 0.4) \times 10^3$   |
| $k_{-1}$ (s <sup>-1</sup> )              | $3.2 (\pm 0.2)$               | $1.5 (\pm 0.1) \times 10^{-1}$ |
| $k_2$ (M <sup>-1</sup> s <sup>-1</sup> ) | $6.3 (\pm 0.5) \times 10^2$   | $1.1 (\pm 0.1)$                |

the rate constants determined, without ever writing an explicit rate equation. A microkinetic approach, writing and solving the differential equations representing the elementary rate steps, would give us this information. To compare the approaches, let us try considering this example without the rate equation. Table 2 gives the values of the six rate constants from scheme 1 determined by Landis and Halpern for the reaction in equation (1) carried out at 298 K. Write each constant down under its appropriate  $k$  variable in scheme 1. Now take a look at these constants in the context of the reaction network shown in scheme 1. In doing so, can we really develop the level of mechanistic insight that is clearly accessible from looking at the rate equations (equations (2) and (3))? Is it easy to get a feeling for the relative concentrations of  $R$  and  $S$  intermediates without equation (2)? Would the rationale for the H<sub>2</sub> pressure effect on ee leap out at you the way it does from equation (3)? There is something both vital and comforting about being able to identify particular terms in the rate equation with the relative concentrations of particular proposed species, and about being able to visualize observed trends on the basis of the rate equation. This approach seems somewhat less divorced from the dynamic concentration profile experimentally obtained and graphically depicted by the rate equation than do rate constants that tumble out of the microkinetic analysis. Part of the recent resurgence in interest in fundamental kinetics [10] stems, I believe, from attempts to bring molecules back into the mathematics. A mechanistic approach to deriving rate equations and using them in an interpretative fashion is central to this concept.

Of course the bottom line in all of this discussion must be the precept that “more relevant information, faster” is what we seek, whatever the means. When we can draw on

microkinetic analysis to provide this, we should do so. And when we can use the framework of a mechanistically based rate equation combined with *in situ* experimental data to aid in our interpretation of a reaction network, we should also welcome this new take on a time-honored approach. Armed with all of these tools, research in both fundamental and applied catalysis in the twenty-first century looks very promising indeed.

## Acknowledgments

D.G.B. is grateful for unrestricted research grants from Pfizer Global Research and Merck Research Laboratories.

## References

- [1] M. Boudart, *Catal. Lett.* 65 (2000) 1–3.
- [2] M. Boudart, *Perspectives in Catalysis* (Blackwell Scientific Publications, Oxford, 1992) p. 183.
- [3] (a) G. Yaluri, J.E. Rekoske, L.M. Aparicio, R.J. Madon and J.A. Dumesic, *J. Catal.* 153 (1995) 65; (b) R.D. Cortwright, J.A. Dumesic and R.J. Madon, *Top. Catal.* 4 (1997) 15.
- [4] J.P. Collman, L.S. Hegedus, J.R. Norton and R. Finke, *Principles and Applications of Organometallic Metal Chemistry*, 2nd ed. (University Science Books, Mill Valley, CA, 1987) pp. 538–541.
- [5] W.S. Knowles, *Acc. Chem. Res.* 16 (1983) 106.
- [6] C.R. Landis and J. Halpern, *J. Am. Chem. Soc.* 109 (1987) 1746.
- [7] This is a statement of the Curtin-Hammett principle, originally developed in the context of understanding the reactivities of conformational isomers. For a comprehensive review, see J.I. Seeman, *Chem. Rev.* 83 (1983) 83–134.
- [8] M. Boudart and G. Djega-Mariadassou, *Catal. Lett.* 29 (1994) 7.
- [9] (a) Y. Sun, R.N. Landau, J. Wang, C. LeBlond and D.G. Blackmond, *J. Am. Chem. Soc.* 118 (1996) 1348; (b) J. Wang, C. LeBlond, C.F. Orella, Y. Sun, J.S. Bradley and D.G. Blackmond, in *Heterogeneous Catal. Fine Chemicals IV*, Stud. Surf. Sci. Catal. 108; H.U. Blaser, A. Baiker and R. Prins (eds.) (Elsevier Science B.V., Amsterdam, 1997) pp. 183–190; (c) Y. Sun, J. Wang, C. LeBlond, R. Reamer, J. Laquidara, J.R. Sowa, Jr., and D.G. Blackmond, *J. Organomet. Chem.* 548 (1997) 65.
- [10] (a) F.G. Helfferich, *Kinetics of Homogeneous Multistep Reactions*, *Comprehensive Chemical Kinetics*, Vol. 38 (Elsevier, Amsterdam, 2001) p.2; (b) Book review of Ref. [9a]; D.G. Blackmond, *Angew. Chem. Int. Ed.* 40 (2001) 4512–4513.