Requiem for the reaction rate equation?

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Received 25 April 2002; accepted 11 June 2002

The utility of the reaction rate expression in aiding in studies of catalytic reactions and in the predictive design and development of catalysts is discussed. This "back to the future" approach is especially valuable in current research in complex multi-phase reactions common to the pharmaceutical industry. The key to this approach is the combination of accurate, continuous experimental data and kinetic modeling of the rate equation.

KEY WORDS: Kinetics; catalysis; rate expressions; organic reactions; *in-situ* reaction monitoring.

1. Introduction

In a *Perspectives in Catalysis* article which appeared recently in *Catalysis Letters*, Professor Michel Boudart hailed a coming revolution in catalytic kinetics [1]. He predicts that the 21st 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 20th 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 variously 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 ensure 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 which 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 temperature over fixed beds of heterogeneous catalysts, which 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

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1011-372X/02/1100-0133/0

Table 1
Comparison of key features of catalytic processes in basic and petrochemical applications with those in fine chemicals and pharmaceuticals.

Feature	Basic chemicals or petrochemical application	Pharmaceutical or fine chemicals applications
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 semi-batch 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

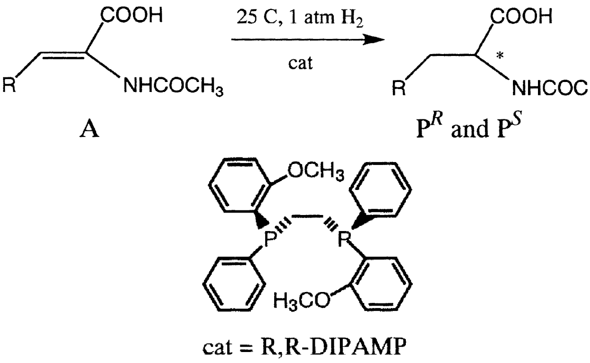
constants for all of these steps, culminating in the presentation of a mechanism-based macroscopic picture of the reaction. For such an approach to be successful, the assembling of the data required entails extensive experimental work, including various *ex situ* adsorption and surface chemistry experiments in addition to 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 which will continue to produce the same products far into the future. This allows plenty of time to think about a catalyst design or modification which may shave a fraction of a percent off costs or increase yield by a minute amount, which translates to a huge economic benefit 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 byproducts are usually minimized by 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 order 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 due to 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 on stream 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 which 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 which 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.



(1)

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 10 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 knowledge of the relative stabilities of intermediate species [7].

Landis and Halpern developed the rate equation shown in equation (2), based on 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 reaction rate data. In addition, this equation helped to 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].

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 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 1 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. I invite you to write each constant down under its appropriate k variable in scheme 1. Now take a look at these constants in the

Table 2

Values of the rate constants in scheme 1 for reactions carried out at 298 K, 1 at H_2, as reported by Landis and Halpern in ref. [6].

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

context of the reaction network shown in scheme 1. In doing so, can we really develop the level of mechanistic insight which 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_2 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 based on the rate equation. This approach seems somehow less divorced from the dynamic concentration profile experimentally obtained and graphically depicted by the rate equation than do rate constants which 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 21st century looks very promising indeed.

Acknowledgments

DGB is grateful for unrestricted research grants from Pfizer Global Research and Merck Research Laboratories.

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