Disguised Chemical Selectivities

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The phenomenon of two or more reactions occurring competitively is familiar to chemists, and there is much interest in the factors that determine *selectivity,* that is, the relative tendencies to form the different products. *Kinetic* chemical selectivity can be defined as the ratio of the rate constants of two competing elementary or complex chemical reactions. It is distinguished from the *thermodynamic* chemical selectivity, which is defined as the ratio of the equilibrium constants of two competing chemical reactions. These ratios are the *intrinsic* chemical selectivities if the rate or equilibrium constants compared refer only to bond-making and bond-breaking events. However, if diffusion or adsorption effects alter the rates of one or both competing reactions, the selectivity is disguised by diffusion or adsorption, respectively.

Chemical Selectivities Disguised by Mass Diffusion

In the present Account only those mass-transport processes will be considered which originate from random thermal motion. The effect of convectional mass diffusion on selectivities will not be discussed in detail. Furthermore, we will focus our attention mainly on solvent-phase reaction systems. Nevertheless, if not stated explicitly, the conclusions derived are also valid for reactions in the gas phase.

For the purpose of rationalizing the path taken by reagents A and B during their reaction to give the product C it is convenient to subdivide a chemical reaction into component processes as shown in Figure 1. At first, solutions of the reacting species A and B have to be mixed together. The dashed-line box shown to be formed in process 1 and to react in process 2 represents the two species mixed but not in contact with each other. The macroscopic diffusion process of mixing is accompanied by a molecular diffusion process in which the encounter complex is formed. Either this encounter complex can dissociate and revert to A and B or bond-making and bond-breaking events can occur, leading to product C.

In most discussions of reaction mechanisms, one is concerned mainly with the question of what occurs *within* this encounter complex. Therefore, kinetic and selectivity studies can only be used to establish these mechanisms if the experimental results represent the intrinsic course of the chemical reaction proper, the bond-making and bond-breaking events. However, in the case of fast reactions this condition is not always fulfilled, as preequilibrium diffusion processes can disguise the kinetics of chemical reactions and hence affect the distribution of products.

The Role of Diffusion Inhibition on Product Distribution. Possible diffusional effects in *isothermal* systems with *steady-state* concentration gradients can be assessed by the Thiele or the Weisz modulus[1-5] (eq 1 and 2). Their disguising effect on the product distribution has been derived explicitly for isothermal *steady-state* systems of competitive first-order reactions.[1,2,6] Such systems are mainly encountered in continuous chemical processes on porous catalysts.

$$\phi = R\sqrt{k/D} \qquad \text{(Thiele modulus)} \qquad (1)$$

$$\Phi = (dn/dt)(1/[A])(R^2/D) \qquad \text{(Weisz modulus)} \qquad (2)$$

For first-order kinetics, ϕ relates the *intrinsic* rate constant, k, with the diffusion coefficient, D, and the characteristic diffusion distance, R. (Analogous expressions have also been developed for higher order kinetics.[1]) The mathematical analysis[1] shows that only in situations where ϕ becomes greater than unity will the intrinsic reactivity be disguised by diffusion effects.

However, if we wish to ascertain the presence or absence of diffusional effects *without knowing* the intrinsic rate constants, the criterion Φ has to be applied.[4] This criterion contains only "observable" quantities such as the observed reaction rate per unit volume, dn/dt, the measurable externally applied reactant

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(1) C. N. Satterfield and T. K. Sherwood, "Role of Diffusion in Catalysis", Addison-Wesley, Reading, Mass., 1965; E. W. Thiele, *Ind. Eng. Chem.,* **31,** 916 (1939); G. Damköhler; *Dtsch. Chem. Ing.,* **3,** 430 (1937); J. B. Zeldovitch, *Acta Physicochim. URSS,* **10,** 583 (1931).

(2) A. Wheeler, *Adv. Catal.,* **3,** 258 (1951); *Catalysis,* **2,** 153 (1955).

(3) E. E. Petersen, "Chemical Reaction Analysis", Prentice-Hall, New York, N.Y., 1965.

(4) P. B. Weisz and C. D. Prater, *Adv. Catal.,* **6,** 143 (1954).

(5) G. Emig, *Fortschr. Chem. Forsch.,* **13,** 451 (1969/70).

(6) J. M. Thomas and S. J. Thomas, "Introduction to Heterogeneous Catalysis", Academic Press, New York, N.Y., 1967; J. G. van de Vusse, *Chem. Eng. Sci.,* **21,** 631 (1966); J. Carberry, *ibid.,* **17,** 675 (1962).

1. Macroscopic diffusion (e.g., convection)

A A A   B B B   A B A

A A A + B B B $\xrightarrow{\text{mixing}}$ B A B

A A A   B B B $\boxed{\text{A B}}$ A

2. Microscopic diffusion (molecular diffusion)

$\boxed{\text{A B}}$ $\rightleftarrows$ (A,B)

encounter complex

3. Reorganization of chemical bonds

(A,B) $\longrightarrow$ C

Figure 1. Component processes in chemical transformations.

concentration, [A], at the boundary of the reactive volume whose characteristic radial dimension is R, and the diffusion coefficient, D, of the reactants. According to Weisz,[4,7] a significant diffusional modification of the chemical reactivity would be expected if Φ exceeds 0.3–3. The Weisz modulus has become an interdisciplinary theorem[8] and has proved invaluable for research and process design.

A mathematical analysis has shown that the measured reactivity and selectivity in *nonisothermal* systems depends not only on the Thiele or the Weisz modulus but also on two additional parameters that allow an appraisal of thermal effects in the systems.[9]

In daily laboratory syntheses, many reactions are performed under *non-steady-state* conditions. Such conditions are encountered, for example, if a reaction is carried out batchwise. Unfortunately, few attempts have been made (for a summary, see ref 19) to describe the influence of diffusion processes on the product distribution under such reaction conditions. In non-steady-state reaction systems, there are at least two situations which may involve diffusion effects. First, the observed kinetics of a chemical reaction can be influenced by the rate of mixing of the reactant solutions (mixing-disguised kinetics). Examples are nitrations with nitronium salts[10] and some bromination, iodination, and azo-coupling reactions of aromatic compounds.[11] Second, the observed kinetics can be determined by the rate of the formation of the encounter complex (encounter rate-determined kinetics). Examples are nitrations with nitric acid,[12] some proton-transfer reactions,[13] reactions of free radicals,[14-16] and the quenching of fluorescence.[15-18]

To avoid misinterpretation of the kinetic data one must specify clearly the influence of these diffusion effects on the substrate and positional selectivity. Whereas the *substrate selectivity* can depend on these diffusional effects, the *positional selectivity,* which determines the relative reactivities of the different positions of ambient reagents (e.g., the ortho:meta: para isomer ratio in aromatic substitutions), is to a first approximation[19] *independent* of mass diffusion occurring *prior* to the encounter complex formation. (This holds in *nonionic* systems if one assumes that no long-range interaction is operating on the reactants. However, in diffusion-limited reactions between *ions* this assumption would seem to be violated, as coulombic interaction might already influence the direction of the approach of the reagent before the solvent cage is formed.)

In order to understand positional selectivities in diffusion-limited reactions, we must appreciate the difference between gas-phase and liquid-phase chemical transformations. Whereas in gas-phase reactions the lifetime of an encounter complex lasts only for one collision, it is estimated[20,21] that an encounter complex of two reactants in most solvents at room temperature survives as many as 10 to 1000 collisions between the reactants before they separate again (cage effect). This collisional motion can be considered as a series of very rapid reflections or vibrations which lead to rotational and translational events within the solvent cage. It is for this reason that, in solution, even when the formation of the encounter complex is the rate-limiting step, positional selectivity is still determined by the different chemical reactivities of the various reaction positions. Only if, in the very extreme case, every collision within the encounter complex were successful in giving the reaction products would we find a statistical distribution of isomers as is found in collision-limited gas-phase reactions.

This different influence of diffusion on substrate and positional selectivities provides one possible explanation for deviations[22] from Brown's reactivity–selectivity relationship. Furthermore, reaction constants such as ρ, ρ^*, α, β as defined by various linear free-energy relationships can also be disguised by diffusion.[23] Therefore,

(7) P. B. Weisz, *Z. Phys. Chem.,* **11**, 1 (1957); *Chem. Eng. Prog., Symp. Ser.,* **55**, 29 (1959).

(8) P. B. Weisz, *Science,* **179**, 433 (1973); *Ber. Bunsenges. Phys. Chem.,* **79**, 798 (1975).

(9) P. B. Weisz and J. S. Hicks, *Chem. Eng. Sci.,* **17**, 265 (1962).

(10) W. S. Tolgyesi, *Can. J. Chem.,* **43**, 343 (1965); S. B. Hanna, E. Hunziker, T. Saito, and H. Zollinger, *Helv. Chim. Acta,* **52**, 1537 (1969); P. F. Christy, J. H. Ridd, and N. D. Stears, *J. Chem. Soc. B,* 797 (1970); J. H. Ridd, *Acc. Chem. Res.,* **4**, 248 (1971); A. Gastaminza and J. H. Ridd, *J. Chem. Soc., Perkin Trans. 2,* 813 (1972); G. A. Olah, *Acc. Chem. Res.,* **4**, 240 (1971).

(11) E. L. Paul and R. E. Treybal, *AIChE J.,* **17**, 718 (1971); P. Eugster, Ph.D. Thesis, ETH, Zürich, 1973; K. Suter, Ph.D. Thesis, ETH, Zürich, 1974; M. Aellen, Ph.D. Thesis, ETH, Zürich (in preparation); E. Crivelli, Ph.D. Thesis, Zürich (in preparation).

(12) S. R. Hartshorn and J. H. Ridd, *Chem. Commun.,* 133 (1967); *J. Chem. Soc. B,* 1063, 1068, (1968), and references therein; J. G. Hoggett, R. B. Moodie, and K. Schofield, *ibid.,* 1 (1969); R. G. Coombes, R. B. Moodie, and K. Schofield, *Chem. Commun.,* 352 (1967); *J. Chem. Soc. B,* 800 (1968); S. R. Hartshorn, R. B. Moodie, K. Schofield, and M. J. Thompson, *J. Chem. Soc. B,* 2447 (1971).

(13) M. Eigen, W. Kruse, G. Maas, and L. de Maeyer, *Prog. React. Kinet.,* **2**, 287 (1964); M. Eigen, *Angew. Chem., Int. Ed. Engl.,* **3**, 1 (1964); *Discuss. Faraday Soc.,* **39**, 163 (1965), and references therein.

(14) L. M. Dorfman and M. S. Matheson, *Prog. React. Kinet.,* **3**, 237 (1965); R. M. Noyes, *J. Phys. Chem.,* **69**, 3182 (1965); *J. Am. Chem. Soc.,* **86**, 4529 (1964); H. S. Johnston and P. Goldfinger, *J. Chem. Phys.,* **37**, 700 (1962); S. J. Lapporte, *Angew. Chem.,* **72**, 759 (1960); R. Klein, M. D. Scheer, and J. G. Waller, *J. Phys. Chem.,* **64**, 1247 (1960); H. W. Melville, *Proc. R. Soc. London, Ser. A,* **163**, 151 (1937).

(15) A. M. North, *Q. Rev., Chem. Soc.,* **20**, 421 (1966).

(16) G. M. Burnett and H. Melville, *Tech. Org. Chem.,* **8**, Chapter 20 (1963); R. M. Noyes, *Tech. Chem., (N.Y.),* **6** (2), Chapter 9 (1974).

(17) B. Williamson and V. K. La Mer, *J. Am. Chem. Soc.,* **70**, 717 (1948); E. J. Bowen and W. S. Metcalf, *Proc. R. Soc. London, Ser. A,* **206**, 437 (1951); R. M. Noyes, *J. Am. Chem. Soc.,* **79**, 551 (1957); Th. Förster, "Fluoreszenz organischer Verbindungen", Vandenhoeck and Ruprecht, Göttingen, Germany, 1951.

(18) R. M. Noyes, *Prog. React. Kinet.,* **1**, 129 (1961).

(19) R. J. Ott and P. Rys, *Helv. Chim. Acta,* **58**, 2074 (1975).

(20) J. Frenkel, "Kinetic Theory of Liquids", Oxford University Press, Oxford, 1946; A. M. North, "The Collision Theory of Chemical Reactions in Liquids", Methuen, London, 1964; E. S. Caldin, "Fast Reactions in Solution", Wiley, New York, N.Y., 1964; W. Jost and K. Hauffe, "Diffusion", Steinkopff Verlag, Darmstadt, 1972, p 91; R. E. Weston, Jr., and H. A. Schwarz in "Fundamental Topics in Physical Chemistry", H. S. Johnston, Ed., Prentice-Hall, Englewood Cliffs, N.J., 1972.

(21) I. D. Clark and R. P. Wayne in "Comprehensive Chemical Kinetics", Vol. II, C. H. Bamford and C. F. H. Tipper, Ed., Elsevier, Amsterdam, 1969, Chapter 4.

(22) P. B. D. de la Mare, *J. Chem. Soc.,* 4450 (1954); F. B. Deans, C. Eaborn, and D. E. Wepster, *ibid.,* 3031 (1959); C. Eaborn and R. Taylor, *ibid.,* 1012 (1961); L. M. Stock and H. C. Brown, *J. Am. Chem. Soc.,* **84**, 1242 (1962).
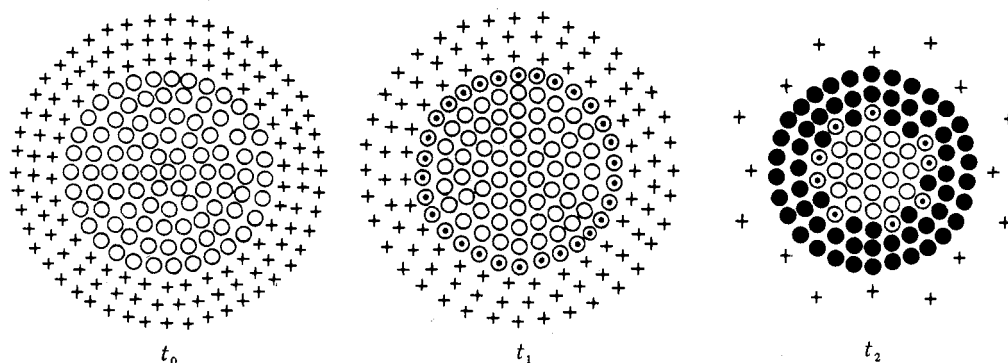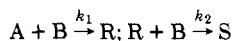
Figure 2. Schematic representation of a mixing-*determined* reaction course for competitive, consecutive, second-order reactions, assuming constant eddy size. t_0, t_1, t_2: reaction times; O, reagent A; +, reagent B; ⊙, primary product R; ●, secondary product S.

$$A + B \xrightarrow{k_1} R; R + B \xrightarrow{k_2} S$$

great care has to be taken in using these experimentally measurable *macro*scopic parameters as an index for *micro*scopic properties, such as transition-state symmetry.[24]

Product Distribution Determined by the Mixing Rate. Coupling of mass diffusion with chemical reactions during the mixing of two reactant solutions has been simulated with the help of a simple model.[19] In order to describe the mixing process occurring during the addition of one solution to another by a model, it is necessary to consider the following processes: (a) addition of one solution to another; (b) eddy diffusion (mechanical transport of the eddies, e.g., by stirring); (c) molecular diffusion (transport processes within the eddy).

If we add a solution of species A to a solution of species B, eddies of solution A in solution B are created. As a first approximation these eddies can be considered as spherical drops with constant mean radius $\overline{R}$. (In reality, $\overline{R}$ decreases with time for miscible solvents. The lifetime of such an eddy can be estimated to be $0.05(\overline{R}^2/D)$, e.g., 0.01 to 1 s). The radius $\overline{R}$ depends on the intensity of the turbulence created by mixing and may be controlled, for example, by mechanical stirring. From the theory of turbulence[25] one can estimate the minimum mean size of such elements of liquid. For the common solvents water, methanol, and ethanol, the mean minimum radius $\overline{R}$ of the eddies in optimal turbulence is approximately 10^{-2} to 10^{-3} cm; this corresponds to an agglomeration of about 10^{12} to 10^{15} molecules. The size of this liquid element increases with increasing viscosity of the solvent. In a mechanically well-stirred solution, the single eddies undergo a fast mutual interchange (a so-called eddy diffusion[26]). Generally, eddy diffusion is much faster than molecular diffusion within the eddy. Consequently the concentrations at the interface of the eddies correspond at any time to those in the surrounding solution.

The general behavior and the dependence of product selectivity on the coupling of mass diffusion with chemical reaction during the mixing process have been simulated and discussed in detail.[19] As an example, in

(23) A detailed discussion is in preparation: P. Rys, *Angew. Chem.*

(24) J. E. Leffler, *Science*, 117, 340 (1953); J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions", Wiley, New York, N.Y., 1963, p 158.

(25) A. N. Kolmogoroff, *C. R. Acad. Sci. USSR*, 30, 301 (1941); J. O. Hinze, "Turbulence", McGraw-Hill, New York, N.Y., 1959; J. T. Davies, "Turbulence Phenomena", Academic Press, London, 1972.

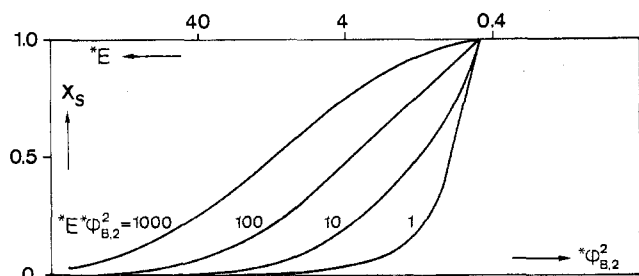(26) P. V. Danckwerts, "Diffusion Processes", Gordon and Breach, London, 1971, Vol. 2.

Figure 2 the mixing-*determined* reaction course of a competitive, consecutive reaction is schematically sketched. For this schematic representation, one of the reactants (e.g., species A) and the resulting products are considered to be immobile in the eddy into which the mobile molecules of the other substance (e.g., species B) penetrate by molecular diffusion: One molecule of A reacts with *two* molecules of B in two reaction stages. One molecule of B can react with a molecule of A only if it can move successfully through the peripheral zone of the R molecules already formed, i.e., if it does not react with the primary product R to give the secondary product S. The probability that this secondary reaction takes place decreases with an increase in the rate of diffusion. In the most extreme case of a mixing-*limited* reaction none of product R but only product S will be found at the end of the reaction, irrespective of the magnitude of the ratio k_1/k_2.

It has been shown[19] that such a system of competitive, *consecutive* second-order reactions coupled with a diffusion process is determined for a given α and given boundary and initial conditions by three parameters: $^*E$, $^*\phi_{B,1}{}^2$ and $^*\phi_{B,2}{}^2$. These are defined by eq 3–5, in which $[A]_0$ and $[B]_0$ are the initial concentration of A and B, respectively (in mol/l.); $\alpha = V_e/V_s$, the ratio of eddy volume V_e to solvent volume V_s; D is the diffusion coefficient of molecules B relative to A (in cm²/s); $\overline{R}$ is the mean minimum radius of the eddies (in cm); k_1 and k_2 are intrinsic (real) second-order rate constants (in M^{-1}/s).

$$^*E = \frac{[A]_0\alpha}{[B]_0} \tag{3}$$

$$^*\phi_{B,1}{}^2 = \frac{\overline{R}^2 k_1[B]_0}{D\alpha} \tag{4}$$

$$^*\phi_{B,2}{}^2 = \frac{\overline{R}^2 k_2[B]_0}{D\alpha} \tag{5}$$

In Figure 3 simulated data are plotted in a manner which allows an easy survey of one's experimental results for 100% conversion. The relative yield X_S is shown as a function of $^*E$ for various $^*E^*\phi_{B,2}{}^2$ and for $^*\phi_{B,1}{}^2/^*\phi_{B,2}{}^2$ (i.e., k_1/k_2) equal to 100. $X_S = [S]/([R] + [S])$ is the normalized fraction of B which reacted to give S. The X_S values which can be obtained, for instance, by varying $[B]_0$ only and keeping $[A]_0$, α, and the mixing conditions constant, all lie on an S-shape selectivity curve whose position along the $^*\phi_{B,2}{}^2$ axis depends only on the value of $^*E^*\phi_{B,2}{}^2$. As a consequence of this, the

Figure 3. Calculated relative yields X_S for 100% conversion as a function of $*E$ for different $*E*\phi_{B,2}{}^2$ values.[27] $*\phi_{B,1}{}^2/*\phi_{B,2}{}^2 = 100$; $\alpha = 4$.
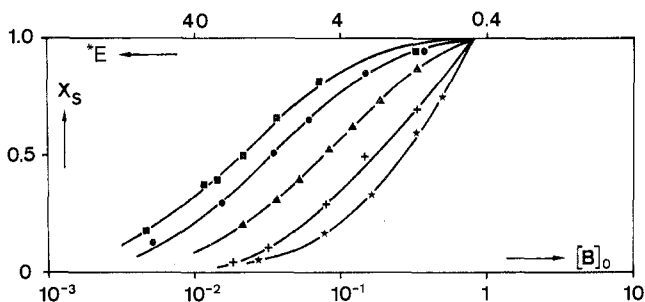

Figure 4. Nitrations of various aromatic compounds (A) with $NO_2{}^+PF_6{}^-$ (B) in nitromethane (20.0 °C) at 100% conversion.[27,28] [A] = 0.1 M; $\alpha = 4$. (■) Prehnitene;[28] (●) durene;[27,28] (▲) mesitylene;[27] (+) m-xylene;[27] (*) p-xylene.[27]

relative k_2 values for different substrates can be found from the relative positions of the respective selectivity curves.

In Figure 4 experimental selectivity curves[27,28] are shown for the consecutive nitration of various aromatic compounds under constant mixing conditions. From their relative positions the following reactivity ratio for the second nitration step can be estimated: prehnitene:durene:mesitylene:m-xylene:p-xylene = 1000: 500:80:10:1. (In the case of m-xylene, interpretation of the experimental data is complicated by the fact that in the primary step more than one mononitro compound is formed.)

Similarly, the mixing-disguised product distribution in competitive, *parallel* reactions has been simulated and discussed in detail.[19] It has also been verified experimentally.[29]

Product Distribution Determined by Encounter Rate. As can be seen from Figure 1 the rate of fast chemical reactions in solution can be affected not only by the mixing process but also by the rate of formation of the encounter complex. Encounter rate-controlled reactions are the fastest possible reactions between initially separated species in solution. Encounter rate constants can be calculated on the basis of various concepts. Reviews of these concepts can be found in several excellent articles[15,18,30] and books.[20,21] Typical values found experimentally for second-order rate constants are 10^7 to 10^9 l. mol^{-1} s^{-1} for radical recombination reactions[14] and as large as 10^{11} l. mol^{-1} s^{-1} for proton-transfer reactions.[13]

Often it is erroneously assumed that all reactions occurring at encounter-controlled rates are so fast that

they can be followed only by special fast reaction techniques such as the temperature-jump method, flash photolysis, NMR line broadening, or sound absorption. However, in bimolecular reactions in which the concentrations of both reagents are very small, the overall rate can be smaller than the mixing rate and can easily be measured by conventional kinetic methods. For instance, the half-life of A in a pseudo-first-order reaction, A + B → C, with B the reagent in excess, is given by $0.693/(k[B])$. For an encounter-limited reaction with a rate constant of 10^9 l. mol^{-1} s^{-1}, this half-life will be greater than 20 s as long as the concentration of B is smaller than 3×10^{-11} mol l^{-1}. Another possibility is that the reagent B might be in rapid equilibrium with another species which is present in large excess. Such situations are found, for example, in nitrating systems,[31,32] where the reagent A is the aromatic substrate and B is the nitronium ion which is in rapid equilibrium with nitric acid.

Product Distribution Determined by Diffusional Motion within the Solvent Cage of an Encounter Complex. A spatial preorientation of reactants within the encounter complex can be decisive for the distribution of products in chemical reactions. This effect has not yet been systematically investigated.

The driving forces leading to an orientation of the reactants within their solvent cage can range from weak van der Waals intermolecular forces, hydrogen bonding, and π-complex formation to covalent bonding. To what extent such an orientation could aid in influencing positional selectivities by diffusional effects has been shown experimentally in intramolecular N-nitro amine rearrangements.[33,34] According to a recent investigation,[34] in the *direct* nitration of 4-phenylazoaniline the nitronium ion attacks the protonated form of the substrate to give mainly nitration in the p' position of the phenylazo substituent. This leads to a positional selectivity which is understood to be mainly determined by the repulsive forces between the positively charged reagents. In contrast, nitration by the *indirect* route through the N-nitro amine occurs mainly via an intramolecular acid catalyzed radical rearrangement. (The N-nitro amine can be regarded as an encounter complex in which the aromatic substrate and the nitrating agent are spatially preoriented for the following C-nitration.) The positional selectivity (ortho:para' ratio) in this rearrangement appears to be determined by the *diffusional motion* of the radical fragments within the solvent cage as it depends on the viscosity of the acidic solvent used. In this case, the intrinsic chemical selectivity does not primarily determine product distribution.

The Selectivity Principle of Polyfunctional Catalysis. A further example of how mass diffusion influences the product distribution of a chemical process can be found in polyfunctional catalyses. Such catalyses occur when, in a multistep chemical reaction, the individual events are catalyzed by different catalysts. In

(27) F. Nabholz, Ph.D. Thesis, ETH, Zürich (in preparation).

(28) F. Pfister, P. Rys, and H. Zollinger, *Helv. Chim. Acta*, **58**, 2093 (1975).

(29) M. Aellen, Ph.D. Thesis, ETH, Zürich (in preparation).

(30) W. Scheider, *J. Phys. Chem.*, **76**, 349 (1972), and references therein; F. C. Collins and G. E. Kimball, *J. Colloid Sci.*, **4**, 425 (1949); T. Koenig, *J. Am. Chem. Soc.*, **91**, 2558 (1969); C. A. Emeis and P. L. Fehder, *ibid.*, **92**, 2246 (1970); K. S. Schmitz and J. M. Schurr, *J. Phys. Chem.*, **76**, 534 (1972).

(31) J. H. Ridd, *Acc. Chem. Res.*, **4**, 248 (1971); R. G. Coombes, R. B. Moodie, and K. Schofield, *J. Chem. Soc. B*, 800 (1968); R. B. Moodie, K. Schofield, and J. B. Weston, *J. Chem. Soc., Chem. Commun.*, 382 (1974); N. C. Deno and R. Stein, *J. Am. Chem. Soc.*, **78**, 578 (1956).

(32) J. G. Hoggett, R. B. Moodie, J. R. Penton, and K. Schofield, "Nitration and Aromatic Reactivity", Cambridge University Press, Cmbridge, 1971, p 27.

(33) W. N. White, H. S. White, and A. Fentiman, *J. Am. Chem. Soc.*, **92**, 4477 (1970).

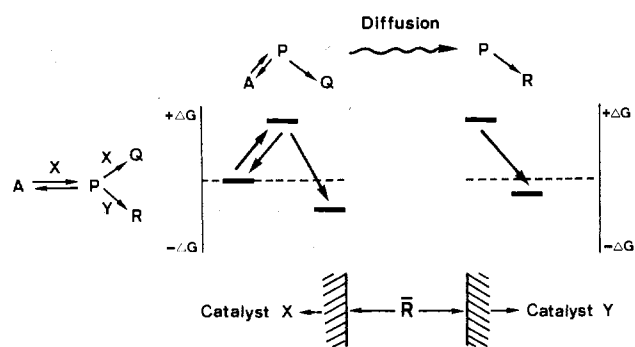(34) H. Hennefeld, Ph.D. Thesis, ETH, Zürich, 1975.

Figure 5. Schematic representation of the principle of polyfunctional catalysis.

order for the whole reaction to proceed, the product of one step has to diffuse as an intermediate from one catalytic function to another.

It was shown[35,36] that the selectivity of such reactions can be determined by a *diffusion-limited* interception of high-energy intermediates, and thus the reaction rate as well as product distribution can depend strongly on the distance between the catalytic functions. This interesting selectivity principle, which is of basic generality and applicability to any multistep reaction system[35] as well as for reactions in living cells, is briefly described in Figure 5.

In several recent studies, polymer-anchored dual-functional catalysts were used in multistep reactions.[37] Polyfunctional catalysis in various scientific disciplines has been reviewed.[8]

Chemical Selectivities Disguised by Adsorption Processes

The term "adsorption process" as used in the following discussion embraces all processes which—in the terminology of a chemist—lead to *complex formation* between the reacting species prior to a chemical transformation. Even the formation of σ-complex intermediates such as Wheland or Meisenheimer complexes in aromatic substitutions can be considered as an adsorption of one reactant onto another by formation of a σ bond.

Apart from covalent bonds, the most important intermolecular forces involved in complex bonding are ion-ion, ion-dipole, hydrogen-bond, van der Waals, charge-transfer, and hydrophobic forces.[38,39] The theoretical treatment of these forces is a matter of very considerable difficulty, particularly in view of the complexities of the molecules involved as well as solvent effects which are not yet well understood. Therefore, we restrict our discussion to one aspect: in the course of a chemical process, complex formation leads to inter-

mediate species in which the spatial orientation of the reactants as well as their lifetime can influence the selectivity of chemical transformations.

Furthermore, for the following discussion it is irrelevant whether π- or σ-bond formation occurs in a single phase or at the phase interface. In the first case one speaks simply of π- or σ-complex formation; in the second case the processes are described by the expressions "physisorption" and "chemisorption", respectively. The borderline between these adsorption processes is arbitrary.

Every bimolecular elementary liquid-phase reaction can be subdivided into (a) the diffusion step of bringing the reactants together to form an adsorption complex AB and (b) the actual chemical transformation which occurs within the confines of this complex (eq 6).

$$A + B \underset{k_{dA}}{\overset{k_{aA}}{\rightleftarrows}} AB \overset{k_{rP}}{\longrightarrow} P \qquad (6)$$
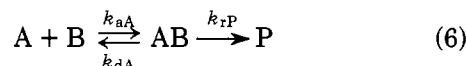
If this reaction obeys the rate equation $d[P]/dt = k[A][B]$, the measurable rate constant k obviously will depend on the rate constants k_{aA}, k_{dA}, and k_{rP} of the individual steps. If the steady-state approximation $|(d[AB]/dt)| \ll |k_{aA}[A][B]|$ applies, then $k = k_{aA}k_{rP}/(k_{dA} + k_{rP})$. For the situation in which $k_{rP}/k_{dA} \gg 1$, then $k = k_{aA}$ (case I). In most practical cases, k_{aA} is the diffusion rate constant.

However, if $k_{rP}/k_{dA} \ll 1$, it follows that $k = k_{aA}k_{rP}/k_{dA}$ (case II). In this case the intrinsic rate constant k_{rP} of the chemical transformation proper can only be evaluated from the measurable rate constant k if k_{aA}/k_{dA} is known. It is also obvious that in case II any structural change resulting in an increase in the stability of AB will only result in an increased k if the rate-limiting transition state is also stabilized. This will be true regardless of whether the interaction is stronger or weaker in the transition state than in the complex AB. In cases where more than one product is formed from the same reactants, any increase in the interaction between the reactants will result in an increased proportion of the product arising via the transition state in which this interaction is stronger.

If (at least) one of the reactants, for instance A, is almost entirely in the complexed form AB (case III), then k_{rP} can be determined without knowing k_{aA}/k_{dA}. The rate is then given by $d[P]/dt = k_{rP}([A]_0 - [P])$, where $[A]_0$ is the total amount of the reactant A introduced into the reaction. In case III, an increase in the attractive interaction between A and B within the complex AB will only lead to an increase in the observable k when the interaction is stronger in the transition state than in the complex AB.

One realizes that the measured overall macroscopic rate constant, and hence in competitive reactions the selectivity, is determined by the microscopic properties of the complex AB, namely the *lifetime* of AB and the *spatial orientation* of the reactants A and B within the complex AB. Various concepts (proximity,[40] propinquity,[41] togetherness,[42] orientation effects,[43,44] orbital

(35) G. A. Mills, H. Heinemann, T. H. Milliken, and A. G. Oblad, *Ind. Eng. Chem.*, **45**, 134 (1953); P. B. Weisz, *Science*, **123**, 887 (1956); P. B. Weisz and E. W. Swegler, *ibid.*, **126**, 31 (1957); P. B. Weisz, *Adv. Catal.*, **13**, 137 (1962); *Nature (London)*, **195**, 772 (1962).

(36) W. O. Haag and D. D. Whitehurst, German Patent 1 800 379 (1968); L. H. Slaugh and J. A. Leonard, *J. Catal.*, **13**, 1385 (1969).

(37) C. U. Pittman, Jr., and L. R. Smith, *J. Am. Chem. Soc.*, **97**, 1749 (1975).

(38) R. Foster, "Molecular Complexes", Vol. I and II, Elek Science, London, 1973-1974.

(39) H. Margenau and N. R. Kestner, "Theory of Intermolecular Forces", Pergamon Press, London, 1969; J. O. Hirschfelder, C. F. Curtiss, and R. B. Bird, "Molecular Theory of Gases and Liquids", Wiley, New York, N.Y., 1954; G. Briegleb, "Elekronen-Donator-Acceptor-Komplexe", Berlin, 1961; H. C. Longuet-Higgins, *Discuss. Faraday Soc.*, **40**, 7 (1965); H. A. Bent, *Chem. Rev.*, **68**, 587 (1968); A. Clark, "The Theory of Adsorption and Catalysis", Academic Press, New York, N.Y., 1970; D. V. Banthorpe, *Chem. Rev.*, **70**, 295 (1970).

(40) A. Dafforn and D. E. Koshland, Jr., *Biochem. Biophys. Res. Commun.*, **52**, 779 (1973), and references therein.

(41) T. C. Bruice, *Enzymes, 3rd Ed.*, **2**, 217 (1970), and references therein.

(42) W. P. Jencks and M. I. Page, *Proc. Meet. Fed. Eur. Biochem. Soc., 8th, 1972* (1972), and references therein; M. I. Page and W. P. Jencks, *Proc. Natl. Acad. Sci. U.S.A.*, **68**, 1678 (1971), and references therein.

$$A + B \underset{k_{dA}}{\overset{k_{aA}}{\rightleftharpoons}} AB \overset{k_{rP}}{\longrightarrow} P$$

$$\underline{\hspace{3cm}}_{k_1}\underline{\hspace{3cm}}$$

$$P + B \underset{k_{oP}}{\overset{k_{aP}}{\rightleftharpoons}} PB \overset{k_{rQ}}{\longrightarrow} Q$$

$$\underline{\hspace{3cm}}_{k_2}\underline{\hspace{3cm}}$$

A, $CH_3NH(CH_2)_6NHCH_3$

B, $D\!-\!SO_2CH\!=\!CH_2$

P, $D\!-\!SO_2(CH_2)_2N(CH_3)(CH_2)_6NHCH_3$

Q, $D\!-\!SO_2(CH_2)_2N(CH_3)(CH_2)_6N(CH_3)(CH_2)_2SO_2\!-\!D$

Figure 6. The influence of the aggregation tendency between reactants on the product distribution in competitive, consecutive reactions.[50] E = $[A]_0/[B]_0$; reaction sequence (see text); solvent: acetone–water 1:19; temperature, 25 °C. (For a negligible aggregation tendency a statistical reactivity ratio of $k_2/k_1 = 0.5$ would be expected if electrostatic repulsion forces are neglected.)

	$[A]_0$, M	D	Aggregation tendency	k_2/k_1
—■— —●—	10^{-5} 10^{-4}		High	120 ± 30 55 ± 4
—*—	10^{-4}		Moderate	1.5 ± 0.2
—▲—	10^{-4} and 10^{-5}		Low	0.5 ± 0.2
—▽—	10^{-4}		Low	0.5 ± 0.2

steering,[40,44,45] rotamer distribution,[46] stereopopulation control[47]) have been introduced in attempts to estimate the contribution of these factors to the rate enhancement in enzymatic and enzymatic-like intramolecular reactions. The matter has been discussed in some detail by Koshland,[40,43] by Jencks,[42,48] and by Bruice.[41,49]

Product Distribution Determined by Preequilibrium Complex Formation. It is possible to demonstrate experimentally[50] for the following reaction system that the relative yield X_P (= $([P] + [PB])/([P] + [PB] + [Q])$) of the primary product and the macro-

scopic reactivity ratio k_2/k_1 are mainly determined by the relative stability (lifetime) of the complexes AB and PB (Figure 6). This relative stability can be varied by changing the residue D. Even though the extent to which the microscopic reactivity of the amine group of P and thus the ratio k_{rP}/k_{rQ} is influenced by the residue D remains to be firmly established, various experimental observations[50] suggest that for this reaction system $k_{rP} \sim 2k_{rQ}$. The statistical factor 2 originates from the fact that the reagent A has two identical amino groups as reaction centers. The observed maximum rate enhancement of 240 is slightly higher than would be expected from the entropy loss due to "unmixing" (loss of independent translational freedom) of the reactants with the environment. This entropy loss corresponds at 25 °C to a change in the activation energy of about 2.4 kcal/mol or a rate enhancement of about 55 for the unimolecular reaction compared to its bimolecular counterpart.

Further studies on the dependence of the product selectivity on the dielectric constant, the ionic strength, and the volume of activation might give valuble information about the properties of AB, such as lifetime and

(43) D. R. Storm and D. E. Koshland, Jr., *J. Am. Chem. Soc.*, **94**, 5815 (1972), and references therein.

(44) P. Deslongchamps, P. Atlani, D. Frehel, and A. Malval, *Can. J. Chem.*, **50**, 3405 (1972); P. Deslongchamps, C. Lebreux, and R. Taillefer, *ibid.*, **51**, 1665 (1973), and references therein.

(45) C. S. Kim and L. L. Ingraham, *Biochim. Biophys. Acta*, **297**, 220 (1973).

(46) T. C. Bruice and U. K. Pandit, *J. Am. Chem. Soc.*, **82**, 5858 (1960).

(47) S. Milstein and L. A. Cohen, *Proc. Natl. Acad. Sci. U.S.A.*, **67**, 1143 (1970).

(48) W. P. Jencks, "Catalysis in Chemistry and Enzymology", McGraw-Hill, New York, N.Y., 1969.

(49) T. C. Bruice, A. Brown, and D. O. Harris, *Proc. Natl. Acad. Sci. U.S.A.*, **68**, 658 (1971).

(50) H. Bosshard, Ph.D. Thesis, ETH, Zürich, 1975.

alignment of the reacting groups.

The Importance of the Spatial Orientation of Reactants for Optimal Selectivity and Reactivity. The role of a precise angular juxtaposition of reactants is nicely demonstrated in recent studies on the stereochemistry of nucleophilic additions to a carbonyl group. The structural pathways for different nucleophiles have been mapped on the basis of crystal structure data.[51,52] They show a striking qualitative agreement with ab initio calculations on the reaction path of the nucleophilic addition of hydride anion to formaldehyde[52,53] on one hand and with the kinetic data of intramolecular lactonizations[43] on the other.

A particular type of reactant orientation has been termed "orbital steering".[49] Chemical reactions are more likely to occur if the orbitals of the electrons involved are oriented in such a way that optimum overlap takes place. Such stereoelectronic effects have been shown experimentally to operate in the selective cleavage of the tetrahedral intermediate in the hydrolysis of amides and esters[44,54] as the bond most readily broken is the one trans-antiperiplanar to the two lone pairs of the other two heteroatoms. Similar conformational requirements appear to be important in the ozonolysis of acetals.[55]

Objections have been raised to the concept that large rate enhancements can be explained by orbital overlap effects alone.[45,56] These objections are based on studies which consider only the static aspects of "orbital steering". Yet, in order to get a more precise picture, the contribution of the dynamic "steering" should also be considered since every molecule takes a different trajectory depending on the direction and the magnitude of its momentum. In this context it is also of interest to speculate about the implications which interreactant complexation may have on the distribution of the reagent energy. This distribution can affect selectivity since for successful endothermic reactions the energy must be present largely as vibration in the bond under attack ("late" transition state), whereas reactant translation is vastly more effective in producing exothermic reactions ("early" transition state).[57] The extent to which this concept can be used to describe the selectivity behavior of reactants within a solvent cage is an open question.

Nonetheless, from what has been said it is obvious that intermolecular reactant/reactant and reactant/catalyst adsorption forces can also disguise the selectivity and specificity of chemical processes by imposing upon the intermediate complex optimal stereoelectronic and conformational effects.

Another structural locking effect was observed in the hydrolysis of dichloroaminotriazines.[58] The kinetic data indicate that aggregation locks the reactant in a tautomeric form which is not the most stable form of the free species but which is the most easily hydrolyzed.

Summary

In this Account the factors which can influence and disguise the selectivity of chemical reactions by diffusion and adsorption processes (complex formation) are discussed. My aim has been to stimulate chemists to make use of these factors in designing selective reactions. In specific examples, product distribution is shown to be influenced by variation of the lifetime of prereaction complexes between the reactants and the spatial orientation of the reactants within these complexes, or by changing the ratio of the rates of the diffusion and the chemical events. Finally, these examples show the danger of drawing conclusions concerning the bond-making and bond-breaking events from observable kinetic data only since these events can be disguised by preequilibrium diffusion and adsorption processes.

(51) H. B. Bürgi, J. D. Dunitz, and E. Shefter, *Acta Crystallogr., Sect. B,* **30**, 1517 (1974); *J. Am. Chem. Soc.,* **95**, 5065 (1973).

(52) H. B. Bürgi, J. D. Dunitz, J. M. Lehn, and G. Wipff, *Tetrahedron,* **30**, 1563 (1974).

(53) H. B. Bürgi, J. M. Lehn, and G. Wipff, *J. Am. Chem. Soc.,* **96**, 1956 (1974).

(54) J. M. Lehn and G. Wipff, *J. Am. Chem. Soc.,* **96**, 4048 (1974); J. M. Lehn, G. Wipff and H. B. Bürgi, *Helv. Chim. Acta,* **57**, 493 (1974).

(55) P. Deslongchamps, C. Moreau, D. Frehel, and P. Atlani, *Can. J. Chem.,* **50**, 3402 (1972).

(56) G. N. J. Port and W. G. Richards, *Nature (London),* **231**, 312 (1971).

(57) J. C. Polanyi, *Acc. Chem. Res.,* **5**, 161 (1972), and references therein.

(58) P. Rys, *Textilveredlung,* **2**, 95 (1967); P. Rys and H. Zollinger, *Helv. Chim. Acta,* **49**, 761 (1966).