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A Singularity Model for Chemical Reactivity

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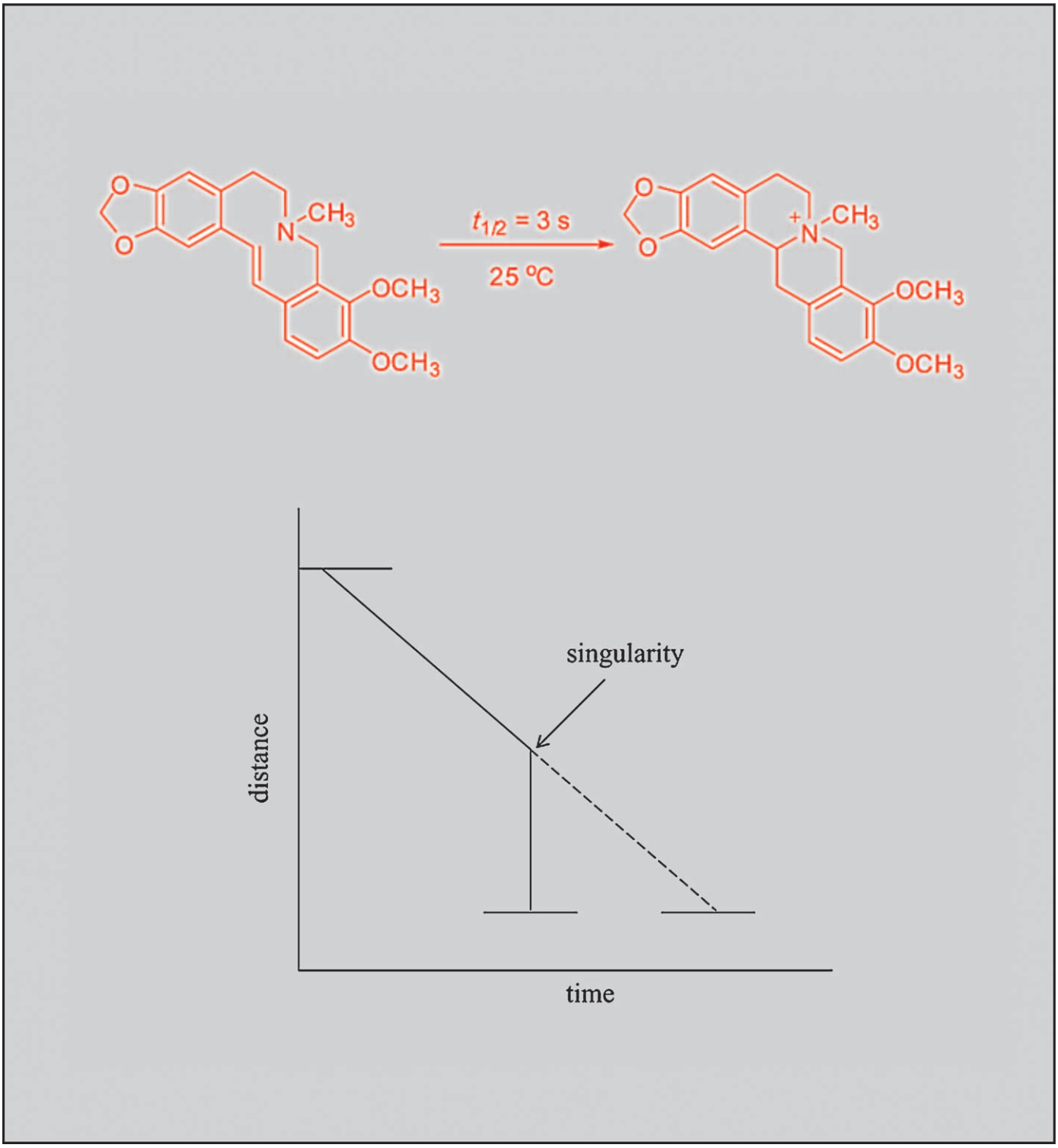

Abstract: This article proposes a model for chemical reactivity that involves singularities ("catastrophes") in the timing of bond-making and bond-breaking events. The common stapler is a good mechanical analogy: As hand-pressure is increased on the machine, the staple hardly changes its configuration until the staple suddenly bends. This is viewed as a singularity or catastrophe, defined classically as an abrupt change resulting from a smooth increase or decrease in external conditions (pressure in the case of a stapler, distance in the case of reactivity). Although experimental observations are provided to support the singularity effect, the model remains a heterodox notion at the present time.

Keywords: catastrophe · chemical reactivity · reaction mechanisms · singularity · transition states

Introduction

Transition states, characterized by bonds in the midst of forming and breaking, are fundamental to any discussion of chemical reactivity.[1–4] A substitution reaction, $Y^- + R_3C{-}Y^* \rightarrow Y{-}CR_3 + Y^{*-}$, illustrates the concept: The reaction passes through the $Y^{\delta-}\cdots CR_3\cdots Y^{*\delta-}$ transition-state in which the partial bond on the left is in the process of forming, and the partial bond on the right is in the process of breaking. In other words, bond formation and bond cleavage occur in a coordinated fashion. We now contemplate the implications of a model in which nucleophile Y^- attacks $R_3C{-}Y^*$, but with little or no initial cleavage of the C–Y* bond. At some point in the trajectory, a critical distance d_c is reached at which any further decrease in the Y–C distance now results in a singularity (or "catastrophe"), namely a precipitous bond formation/cleavage reaction. One possible singularity formalism is given in Equation (1) in which the // symbol within encounter complexes $[Y^-//R_3C{-}Y^*]$ and $[Y{-}CR_3//Y^{*-}]$ denotes a critical distance between the reacting atoms. The central carbon atom need not necessarily experience a pre-catastrophe configurational alteration as Y^- approaches the carbon.

$$Y^- + R_3C{-}Y^* \rightarrow [Y^-//R_3C{-}Y^*] \rightarrow [Y{-}CR_3//Y^{*-}] \rightarrow Y{-}CR_3 + Y^{*-} \quad (1)$$

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The common stapler is a good mechanical analogy of the preceding singularity mechanism. As hand pressure is increased on the machine, the staple hardly changes its configuration until the staple suddenly ("catastrophically") bends and, in so doing, bonds two sheets of paper together. By a singularity (or "catastrophe") is meant an abrupt change resulting from a smooth increase or decrease in external conditions (pressure in the case of a stapler, distance in the case of reactivity).[5,6] At this point in time, applying singularity events to chemical reactivity should be considered merely an intriguing "thought-exercise". However, experimental data support the presence of catastrophic mechanisms, and these will be cited once the model and its ramifications are described in more detail.

The Model

Figure 1 shows a plot of the free energy against the distance between nucleophile and electrophilic carbon according to a speculative Equation (1). In the forward reaction, the Y–C

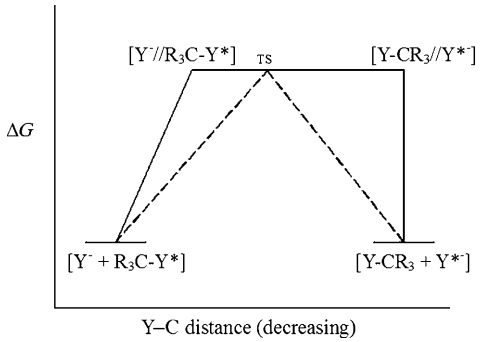


Figure 1. An energy profile in which free energy is plotted vs. Y/C distance for $Y^- + R_3C{-}Y^* \rightarrow Y{-}CR_3 + Y^{*-}$ in which Y = Y*. The transformation of $[Y^-//R_3C{-}Y^*]$ into $[Y{-}CR_3//Y^{*-}]$ constitutes a singularity. The dotted line indicates a conventional transition-state plot.

distance decreases along the *x* axis from left to right. In the reverse reaction, the Y*–C distance decreases from right to left. High up on the profile the encounter complexes, $[Y^-//R_3C{-}Y^*]$ and $[Y{-}CR_3//Y^{*-}]$, have equal energies when the nucleophile Y and leaving group Y* are identical. The horizontal tie-line connecting the two complexes, each at its critical distance, implies that their interconversion is without activation energy and extremely fast. Also included in Figure 1 is the classical transition-state model (dotted line). The difference between this classical model and the singularity model is substantial: In contrast to the former, the singularity model does not involve a Y* that continuously and smoothly departs from the carbon atom when Y^- approaches that carbon atom. Instead, the singularity model

implies that forward displacement occurs precipitously when, and only when, the system possesses sufficient energy for Y^- to reach a critical distance d_c from the electrophilic carbon. Thus, the difference between the singularity model and conventional thought lies mainly in the timing of events.

Note that the asymmetry of the singluarity plot in Figure 1 does not mean that the principle of microscopic reversibility has been violated. The forward reaction (with the Y–C distance as the coordinate) and reverse reaction (with the C–Y* distance as the coordinate) have mirror-image profiles, the main point being that Y–C formation and C–Y* cleavage are partially uncoupled.

Consider now the case of a simple bond-forming reaction, A + B → A–B. Reaction coordinate diagrams, lacking time as a variable, give no information as to the time-dependence of bond formation. Hence, we often prefer to visualize singularity processes using a distance versus time plot (Figure 2).

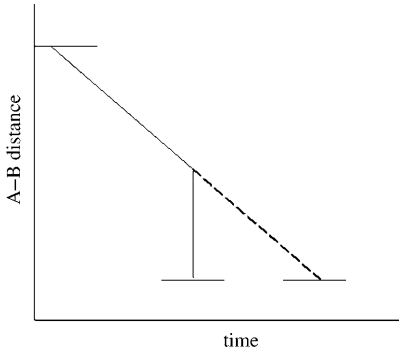


Figure 2. A distance versus time plot for the A + B → A–B reaction according to a singularity model (solid line) and non-singularity model (dotted line).

The A/B bond length is seen to decrease gradually with time, because desolvation of the reactants, in addition to the inevitable "reverse" escape of the reactants from each other's proximity, tend to retard the reaction. However, when d_c is ultimately reached, the fully formed covalent bond appears abruptly as indicated by the vertical drop in the distance versus time plot. This is in contrast to a continuously developing A/B bond (dotted line). Distance versus time plots, despite their potential importance to kinetics, are far less common in the literature than those ubiquitous potential energy surfaces.[7–9]

Now if the principle of microscopic reversibility is to be respected, then Figure 2 also defines the reverse reaction, namely A–B → A + B. Moving from right to left in Figure 2 reveals that the A–B bond stretches until it reaches d_c after which a slower separation of A and B take place. In other words, small A–B separations occur rapidly until a point is reached where fragmentation creates a need for appreciable solvation reorientation, and thus the fragments depart from each other more slowly.

Let us return to an identity-substitution as in Equation (1) and Figure 1, but in which Y becomes both a better nucleophile and leaving group.[10] Other factors being equal, the resulting energy profile is assumed to resemble Figure 1 except that it is cropped at the top (Figure 3). Clearly, the

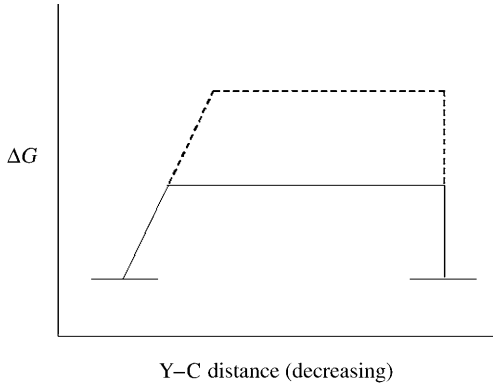


Figure 3. A free energy diagram as in Figure 1 except that Y = Y* is now a better nucleophile/leaving group than in the original (dotted line).

point of "catastrophe", that is, where actual bond formation/cleavage suddenly occurs, corresponds to a longer nucleophile–carbon distance than in Figure 1 (recall that the x scale decreases from left to right). Thus, Y^- need not approach the carbon atom as closely in Figure 3 as in Figure 1 in order to precipitate the subsequent bond-altering events. Since d_c has increased in length, the energy requirements associated with atomic repulsions are diminished, and the reaction proceeds faster than in Figure 1. Note that the "tie-line", connecting the two high-energy encounter complexes, now reflects a larger difference between the long Y^-–C distance in $[Y^-//R_3C–Y^*]$ and the short Y–C distance in the intact Y–C bond. The corresponding effect in traditional chemistry would be called "an earlier transition state." A useful generalization, that we will make use of later, arises from the preceding considerations: In a series of related bimolecular reactions, the faster the reaction the longer the critical distance d_c.

For many years we have been extolling the virtues of "spatiotemporal theory" for the mechanism of enzyme action.[11–23] Since the mechanism postulates a close relationship between the speed of enzymatic reactions and geometric (distance) parameters,[24] the singularity model is relevant to the theory. How exactly might an enzyme accelerate a reaction according to the singularity model? Two routes are envisioned (see route 1 and route 2 in Figure 4). In route 1, the tie-line connecting the two d_c states is lowered. This might occur, for example, if the enzyme coordinates Y* of $R_3C–Y^*$ to an electrophilic species at the active site (i.e., $R_3C–Y^*\cdots E^+$). By rendering Y* a better leaving group, the critical distance necessary for the forward reaction would be expected to increase (again reflecting the principle that a faster reaction leads to a longer d_c). Accordingly, the activation energy decreases from [A + B] to [B]. Route 2 effects catalysis by an entirely different mechanism. In this case, Y^-

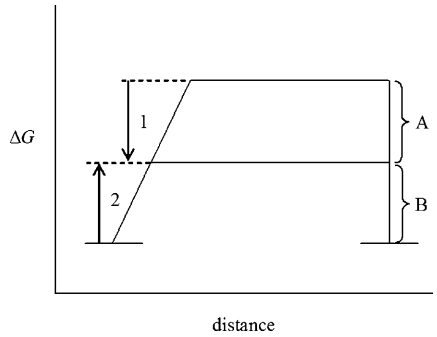


Figure 4. Two ways in which an enzyme might accelerate the reaction in Figure 1.

and $R_3C{-}Y^*$ at the active site are forced to reside at a shorter $Y^{-}{-}C$ distance in the ground state, while maintaining the original d_c. The activation energy now decreases from [A+B] to [A]. The energy required to "activate" the reactants is supplied (to borrow from an old idea from the literature)[25] by sacrificing non-covalent binding of the reactants to the enzyme. Naturally, a combination of routes 1 and 2 is possible.

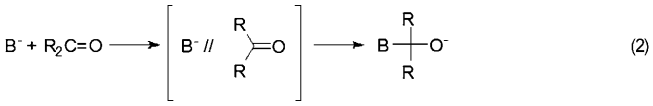
Route 1 accelerates the reaction by lengthening d_c, whereas route 2 accelerates the reaction while keeping d_c constant. In other words, whereas route 1 creates a longer critical distance with a lower energy requirement, route 2 maintains the original critical distance but reduces the energy to reach it. Although route 1 is reminiscent of transition-state stabilization (to which enzyme catalysis has been classically attributed), route 1 and transition-state stabilization are in fact rather different. Unlike transition-state stabilization, route 1 does not require us to envision the enzyme engaged in a 10^{14}–$10^{24}\,M^{-1}$ binding of a species, the lifetime of which lies at the vibrational limit and the structure of which is replete with partial bonds. Instead, route 1 involves a discrete encounter complex in which "catastrophic" bond formation/cleavage takes place at a longer d_c and lower energy, but it is route 2 that corresponds most closely to spatiotemporal theory: An enzyme is thought to impose shorter distances upon the reacting groups, thereby shifting the system closer to the relevant critical distance at which reaction singularities take place. Since a water molecule placed between two reacting atoms would prevent the atoms from attaining d_c, and since the diameter of a water molecule is about 3 Å, it is presumed that critical distances must be less than 3 Å. Stated in another way, desolvation must be an important element of all solution processes, including those of enzymes, a fact that is generally recognized in whatever model is invoked.

Perhaps the time has come to address important questions that have undoubtedly arisen in the minds of readers. What might be possible causes for the presence of singularities? Are singularities at least reasonable if as yet unproven? One possible model qualitatively views reactivity as analogous to a phase change such as melting. In melting, a cooperative reorganization[26–28] involving a large number of atoms leads to a sudden phase change (characterized by a sharp melting point of the bulk material) when sufficient energy is supplied. Actually, the number of species required for a singularity need not be very large. For example, only fifty surfactant molecules are needed to cooperatively and abruptly self-assemble into a micelle once a "critical micelle concentration" is reached.[29] Since in a chemical reaction a large number of electrons, atoms, and solvent molecules must cooperatively alter their disposition and/or energies, one might reasonably postulate a phase-change type of singularity in reaction kinetics when critical distances and their corresponding energies are attained. The analogy of a chemical reaction to a phase change is new and speculative, but worthy of considerable further thought.

Let us now consider a simple proton-transfer reaction to a base from a carbon acid: $B^- + H{-}CR_3 \rightarrow BH + {}^-CR_3$. Two possible singularity domains (encompassing either time or distance as dependent variables) can be envisioned: 1) There might be a sharp break in the distance versus time function. Thus, partial proton transfer occurs gradually followed by a sudden and total transfer to form products BH and $^-CR_3$. 2) Alternatively, B^- approaches $H{-}CR_3$ with little or no cleavage of the $H{-}CR_3$ bond until, at the critical distance, the proton-transfer occurs "catastrophically" (recall the staple machine!). It might be argued that this second model must be false, because it fails to explain why the reaction displays an $H{-}CR_3/D{-}CR_3$ isotope effect, as it would be expected to do.[30] After all, since H–C or D–C cleavage is not actually involved in the pre-catastrophe (and rate-determining) events, why would there be an isotope effect? Yet a $k_H/k_D > 1.0$ isotope effect can be explained by making the reasonable assumption that the critical distance in $[B^-//H{-}CR_3]$ is longer than that in $[B^-//D{-}CH_3]$. Therefore, less energy is required to break the bond to the hydrogen than to the deuterium.

Addition of a nucleophile B^- to the carbonyl group of $R_2C{=}O$ proceeds according to Equation (2). It is possible to envision in this reaction a distortion (lengthening) of the carbonyl group within a pre-catastrophe encounter complex. If this is true, then the transition-state and singularity models overlap, and the distinction between the two becomes fuzzy. In other words, there is no reason to suppose that the two models are mutually exclusive. There may, after all, be a subtle interplay between continuity and discontinuity in which a singularity occurs within a distorted substrate. Once again, the singularity is best considered from the point of view of distance and time. Thus, approach to the critical distance is a continuous function of time followed by a "catastrophic" formation of an intact bond between the base and carbonyl carbon atom. Although the structure at the critical distance and the structure of the transition-state may be identical, there is an important difference in emphasis. With the critical distance concept, the focus is (as the term implies) on the distance between reactants and the timing of the resulting bond changes; with transition-state theory, in which the emphasis is on energy—timing is not a factor. It might be said that singularity theory involves ki-

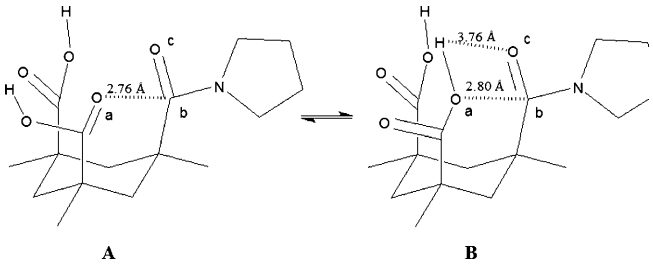
netic concepts, whereas transition-state theory is mainly thermodynamic in origin.



(2)

Experimental Support

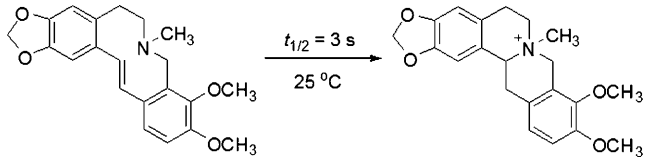
The singularity model and its spatiotemporal partner predict that enzyme-like rates should be observed with organic systems that rigidly hold a nucleophile and electrophile at a distance at or near the critical distance. Of the many "enzyme models" that attest to this expectation, one of the most striking involves an intramolecular-catalyzed cleavage of an aliphatic amide (Scheme 1).[14] Now an aliphatic amide



Scheme 1.

is a difficult functionality to hydrolyze; a ten-hour reflux in concentrated HCl is not unusual. However, when a carboxyl group is held in a 1,3-diaxial relationship to the amide, the amide cleavage occurs with a half-life of 8 min at neutral pH and 21.5 °C. (Note that although the structure above has two carboxyl groups, only a single carboxyl is needed for the observed enzyme-like rate acceleration, the other carboxyl being merely a "spectator".) MM2-based calculations show conformations **A** and **B** in which either a carbonyl oxygen or a hydroxyl oxygen is held at a contact distance of 2.8 Å from the amide carbonyl carbon. A distance of 2.8 Å is less than the diameter of water, but close to the van der Waals contact distance of the reacting atoms. Moreover, in both cases the nucleophilic oxygen lies above the plane of the amide group as is necessary for proper orbital overlap. In conformation **B**, the carboxyl group is poised for synchronous nucleophilic attack and proton delivery, which is consistent with experimental evidence indicating that proton transfer plays a key role in the rate-determining step. The results demonstrate that an enzyme need not employ an esoteric mechanism (e.g., "vibrational activation") in order to cleave a poorly reactive entity, such as an aliphatic amide. If the enzyme merely positions a carboxyl group above the amide carbonyl with a distance approximating d_c, most of the necessary catalytic power of a protease would be achieved.

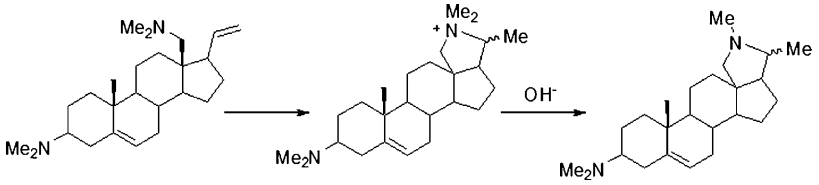
A second instructive "enzyme model", among the multitude available, deals with the addition of an amine to an unactivated double bond (Scheme 2).[31] This reaction has a



Scheme 2.

half-life of 3.3 s at 25 °C in basic 20 % dioxane–water. The corresponding intermolecular reaction has never been observed, which is hardly surprising given that electron-rich double bonds are normally subject to attack by electrophiles, not nucleophiles. Something special is evidently imparting an enzyme-like rate acceleration to the cyclic system. Although a water molecule might conceivably donate a proton to the developing carbanion, weak general-acid catalysis of this type should be only a minor contributor to the huge rate enhancement. Far more important seems to be the relief of ground-state strain when the nitrogen–carbon bond is formed. This explanation can be couched in terms of the singularity model of chemical reactivity: The distance between the nitrogen and the relevant carbon is somewhat less than the 3 Å sum of the van der Waals radii (too short for an intervening water molecule). Thus, the ring structure imposes the critical distance d_c, or something close to it, upon the amine and receptor carbon, and the ring system "snaps shut" in an otherwise highly improbable reaction.

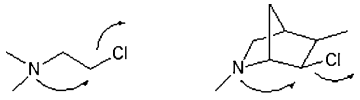
If the concept of a reaction singularity is correct, then one would expect a modest decree of conformational freedom in an intramolecular framework to have a major deleterious effect on the rate. Even a single free rotation would allow the reacting atoms to escape the imposition of a pre-singularity critical distance. For example, the amino-alkene in Scheme 3 cyclizes only upon heating for 6 h at 150 °C.[32] Compare this rate to the 3.3 s at 25 °C, mentioned above, for the system in which the ability to escape the critical distance is denied.



Scheme 3.

The singularity model is not as static as might be assumed from the previous remarks. Even a highly constrained system possesses a measure of flexibility that allows the critical distance to be achieved regularly and often, but not usually continuously. Thus, an observed rate reflects a distribution of rates only one of which, at the critical distance, is essentially instantaneous. The more often the critical distance is achieved per unit time, the higher the overall reaction rate.

It should be noted that there is a mechanistic similarity between the imposition of a critical distance upon an intramolecular system and the old idea that fast intramolecular reactions reflect relief of ground-state strain. Differentiating the critical distance concept from strain-relief (which is a perfectly legitimate source of rate enhancements) is crucial if the critical distance mechanism is to be taken seriously. Fortunately, there exist kinetic data that allow us do exactly this. Compounds **A** and **B**, for example (Scheme 4), engage

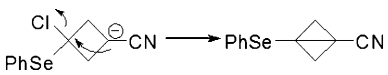


A $k_{rel} = 1$ **B** $k_{rel} = 2 \times 10^5$

Scheme 4.

in intramolecular Sn2 displacements.[33] Although both reactions create strained systems, the strain produced in **B** greatly exceeds that produced in **A**. Thus, we have systems predicting that: 1) **A** will react faster than **B** if strain effects dominate the kinetics and 2) **B** will react faster than **A** if imposition of a critical distance dominates the kinetics. The latter prediction follows from the fact that the bicyclic ring structure in **B** imposes an "inescapable" critical distance, or one very close to it, upon the reacting atoms. In contrast, free rotations in **A**, especially around the lone C–C bond, release the molecule from such constraints. As seen, **B** reacts 2×10^5 faster than **A** despite the enhanced strain created in the reaction of **B**, thereby strongly supporting a critical distance effect and the resulting singularity. The lesson here is that one cannot casually dismiss fast rates at close contact distances as "relief of strain" (as is common practice). Since strain in the reaction of **B** is in fact produced rather than relieved, its relative reaction rate would undoubtedly have been far greater than the observed 2×10^5 if one adjusted for the deleterious strain effect.

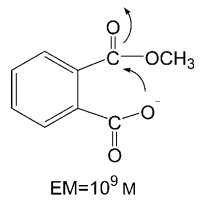
Displacement across a cyclobutane ring also differentiates distance effects from relief of strain.[34] The reaction in Scheme 5 occurs with a remarkable rate of $3 \times 10^{10}\ s^{-1}$. Now



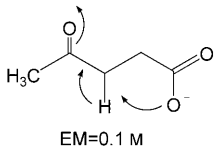
Scheme 5.

the strain energy of cyclobutane is about $27\ kcal\,mol^{-1}$, whereas that of bicylobutane is about $66\ kcal\,mol^{-1}$. Although $39\ kcal\,mol^{-1}$ strain energy is generated in the displacement, the reaction proceeds at a rate that can be classified as "catastrophic". The remarkable rate can be ascribed to the short contact distance that eclipses the accompanying production of strain.

An "effective molarity" ($EM = k_{intra}/k_{inter}$) has been used to quantify the comparison between the rates of an intramolecular reaction and its intermolecular counterpart.[35] (Formally, EM equals the concentration of excess reactant needed to make an intermolecular reaction proceed at the observed rate of the intramolecular process.) For example, $EM = 10^9$ M for the cyclization of the phthalate monoester to phthalic anhydride (Scheme 6), indicating that this intramolecular carbonyl reaction possesses a huge rate advantage relative to an intermolecular analog (e.g., benzoate ester plus benzoate). Strangely, however, intramolecular proton-transfer reactions are, with only a few exceptions, most often characterized by low EM values. An example is shown below (Scheme 7). Thus, joining the base unit to the carbon-acid nets very little in the way of rate benefit.[36] The question arises as to why intramolecular proton-transfers are slow, while intramolecular carbonyl additions are fast, compared with their intermolecular counterparts. This question is key to the understanding of intramolecularity and, by analogy, to the understanding of enzymes.



Scheme 6.



Scheme 7.

The traditional explanation for low EM values of intramolecular proton transfers invokes "loose" transition states that minimize the entropic advantage of intra- over interprocesses.[35] Our singularity model offers a different point of view. The $EM = 10^9$ M for the phthalate reaction indicates that the intramolecular framework holds the carboxylate at or near the critical distance for carbonyl addition. On the other hand, the EM = 0.1 M for the general base enolization indicates that the carboxylate is nowhere near the critical distance from the proton. Geometric factors support the latter assertion. Thus, proton transfers are fastest when the B⁻···H–A geometry is linear.[37] Proton transfer can also occur at sizeable departures from linearity (as seen in the above keto acid), but the rates are correspondingly slower and, therefore, the critical distances should be shorter. To reach such a short critical distance in the keto acid, in which a singularity can take place, there must be bond-bending that adds to the activation energy and detracts from the rate advantage relative to the intermolecular reaction between a ketone and acetate. This geometrically based rationale

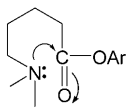
avoids discussion of entropy and the corresponding ill-defined "looseness" concept.

No theory is worthwhile unless it can make testable predictions. In this light we now predict the relative EM of two intramolecular reactions in which a particular nucleophile attacks two different electrophiles such as an ester and an amide. Since an ester is inherently more reactive than an amide, it is reasonable (given the preceding discussion) that the ester has a longer critical distance, designated $d_c(e)$, than the critical distance for the amide, designated $d_c(a)$. Now if a rigid carbon skeleton holds the nucleophile at a distance D (and a Burgi–Dunitz angle of 105°) above the carbonyl of both the ester and amide, then three possibilities present themselves: 1) $D > d_c(e)$ and $d_c(a)$, 2) $d_a(a) < D < d_c(e)$, and 3) $D < d_c(e)$ and $d_c(a)$. EM values expected from these three relationships are given in Table 1.

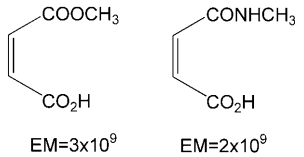
Table 1. Kinetic consequences of different geometries.

Distance	EM of Ester	EM of Amide
$D > d_c(e)$ and $d_c(a)$	small	small
$d_c(a) < D < d_c(e)$	large	small
$D < d_c(e)$ and $d_c(a)$	large	large

In case 1, EM values for both the ester and amide are small because strain and torsional effects, necessary to distort the molecules into their critical distances, will contribute to the activation energy. Case 2 is by far the most interesting situation because the imposed distance exceeds the singularity requirements for the amide but not for the ester. In such an event, the EM should be much larger for the ester than for the amide. Although systematic studies that test this hypothesis are rare, there are data supporting the predictions. For example, when Ar is switched from phenyl to 4-nitrophenyl in the system below (Scheme 8), the EM increases from 490 to 2330. No doubt the increase would have been much larger if the intramolecular system had rigidly held the amine group within the critical distance of the *p*-nitrophenyl compound, but outside the critical distance of the phenyl analogue. Conformational freedom, as we saw earlier, is the enemy of imposed critical distances. An example of case 3, in which the intramolecular nucleophile presumably lies within the critical distance for both the ester and the amide, is given below in Scheme 9.



Scheme 8.



Scheme 9.

A reaction leading to two products is usually assumed to involve two mechanistic pathways with two different transition states. Recently, however, an alternative has been advanced, namely a single transition state that "bifurcates" into two distinct products.[38,39] Such a possibility is predicated not on the energetics of the transition state per se, but rather on the shape of the potential energy surface in the region of the transition state. The singularity model provides alternative explanation: If the two reactive sites on the same substrate are in proximity (e.g., the proton and the carbon in competing E2-elimination/Sn2-substitution reactions), then a single reagent molecule (e.g., a base/nucleophile) might simultaneously meet the critical distance requirements for both reactions, in which case two products will be observed.

Models are to be used, not believed. This principle is no better illustrated in organic chemistry than with resonance theory. Actual belief in the reality of resonance contributors is, in a sense, immaterial. The important point is that the resonance concept is so useful in rationalizing the behavior of organic molecules that every organic chemist must have a command of the concept. As we saw above, the singularity model is also capable of explaining many aspects of organic reactivity, and this alone justifies contemplation of the model. However, the fact remains that computed potential energy surfaces do not generally reveal the presence of singularities. There are three possible reasons for this: 1) An absence of singularities in theoretical modeling of reaction surfaces might reflect, in part, the smooth mathematical potential functions that underlie the computations (their output being unable to escape the constraints of the software). 2) Energy profiles may not often reveal, by their very nature, singularities that would be evident in distance versus time plots (were these only available!). 3) It can be seen in Figure 1 that when d_c is shortened relative to the Y–C bond length, the tie-line connecting the two encounter complexes is also shortened. If Figure 1 is thereby sufficiently "sharpened", the singularity and transition-state models will be difficult to differentiate using free energy plots alone.

Conclusions

In conclusion, we have set forth the idea that singularities are a component of reaction pathways. Experimental data were cited to show that the proposal has considerable explanatory power. The question remains, of course, as to the generality of the mechanism and, indeed, of the very existence of singularities in reaction kinetics. Since singularities in kinetics are at this point merely an abstraction attempting to reach the articulate surface through this essay, we cannot answer the question. This much seems certain. Physical chemists must pay more attention to the time-course of reaction pathways.[40] Potential energy surfaces, useful as they are, will not solve the problem. To give an analogy: a 100-mile car trip should be described not only by the amount gas needed for the trip (the energetics of the situation), but

by the amount of time required to travel, say, each ten-mile segment. The ten time values clearly need not be identical. In fact, if the final ten miles were covered five times faster than any of the previous ten-mile segments, this could be considered a "singularity" of the type that might also be present, metaphorically speaking, in reaction pathways.

Analyses of reaction pathways must take into account the passage of time,[41,42] especially the elusive and all-important time-lag between cause and effect. It can come as no surprise that the arguments presented here are, as is common in the initial stages of an idea, rather qualitative in nature, but they can be expected to be tested more quantitatively in the future. Thus, chemical reactions might join earthquakes, avalanches, market crashes, epidemics, heartbeat, and bridge failures as belonging to natural phenomena with unstable critical states.

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[1] H. Eyring, *J. Chem. Phys.* **1935**, *3*, 107.
[2] L. Pauling, *Am. Sci.* **1948**, *36*, 51.
[3] W. P. Jencks, *Current Aspects of Biochemical Energetics* (Ed.: E. P. Kennedy), Academic, New York, **1966**, p. 273.
[4] E. V. Anslyn, D. A. Dougherty, *Modern Physical Organic Chemistry*, University Science Books, Sausalito, **2006**.
[5] V. I. Arnold, *Catastrophe Theory*, 3rd ed., Springer, Berlin, **2004**.
[6] P. G. Drazin, *Nonlinear Systems*, Cambridge University Press, Cambridge, **1992**.
[7] Z. Xie, B. J. Braams, J. M. Bowman, *J. Chem. Phys.* **2005**, *122*, 224037.
[8] D. De Fazio, V. Aquilanti, S. Cavalli, A. Aquilar, J. M. Lucas, *J. Chem. Phys.* **2008**, *129*, 064303.
[9] D. H. Nouri, D. J. Tantillo, *Tetrahedron* **2008**, *64*, 5672.
[10] P. R. Wells, *Chem. Rev.* **1963**, *63*, 171, p.212.
[11] F. M. Menger, *Pure Appl. Chem.* **2005**, *77*, 1873.
[12] F. M. Menger, A. L. Galloway, D. G. Musaev, *Chem. Commun.* **2003**, 2370.
[13] F. M. Menger, *Acc. Chem. Res.* **1993**, *26*, 206.
[14] F. M. Menger, M. Ladika, *J. Am. Chem. Soc.* **1987**, *109*, 3145.
[15] F. M. Menger, K. Gabrielson, *J. Am. Chem. Soc.* **1992**, *114*, 3574.
[16] M. J. Sherrod, F. M. Menger, *Tetrahedron Lett.* **1990**, *31*, 459.
[17] F. M. Menger, *Biochemistry* **1992**, *31*, 5368.
[18] F. M. Menger, M. J. Sherrod, *J. Chem. Soc. Perkin Trans. 2* **1988**, 1509.
[19] F. M. Menger, *Acc. Chem. Res.* **1985**, *18*, 128.
[20] F. M. Menger, L. E. Glass, *J. Am. Chem. Soc.* **1980**, *102*, 5404.
[21] F. M. Menger, *Adv. Mol. Model.* **1988**, *1*, 189.
[22] F. M. Menger, U. V. Venkataram, *J. Am. Chem. Soc.* **1985**, *107*, 4706.
[23] F. M. Menger, J. F. Chow, H. Kaiserman, P. C. Vasquez, *J. Am. Chem. Soc.* **1983**, *105*, 4996.
[24] The notion of *near attack conformation* was introduced by T. C. Bruice subsequent to spatiotemporal concepts and, in fact, it embodies the same general idea of ground state orientation as a key element of reactivity. The term has stuck and is now often used in place of the more prosaic *proximity*. Singularities as such were never a component of NAS. T. C. Bruice, F. C. Lightstone, *Acc. Chem. Res.* **1999**, *32*, 127.
[25] D. A. Kraut, K. S. Carroll, D. Herschlag, *Annu. Rev. Biochem.* **2003**, *72*, 517.
[26] J. M. Gibbs-Davis, G. C. Schatz, S. T. Nguyen, *J. Am. Chem. Soc.* **2007**, *129*, 15535.
[27] S. Y. Park, J. M. Gibbs-Davis, S. T. Nguyen, G. C. Schatz, *J. Phys. Chem. B* **2007**, *111*, 8785.
[28] J. Becaud, I. Pompizi, C. J. Leumann, *J. Am. Chem. Soc.* **2003**, *125*, 15338.
[29] K. Holmberg, B. Jönsson, B. Kronberg, B. Lindman, *Surfactants and Polymers in Aqueous Solution*, 3rd ed., Wiley, New York, **2003**, Chapter 2.
[30] E. V. Anslyn, D. A. Dougherty, *Modern Physical Organic Chemistry*, University Science Books, Sausalito, **2006**, Chapter 8.
[31] A. J. Kirby, C. J. Logan, *J. Chem. Soc. Perkin Trans. 2* **1978**, 642.
[32] H. Favre, R. D. Haworth, R. D. J. McKenna, R. G. Powell, G. H. Whitfield, *J. Chem. Soc.* **1953**, 115.
[33] R. O. Hutchins, L. Rua, *J. Org. Chem.* **1975**, *40*, 1811.
[34] U. Habusha, E. Rozental, S. Hoz, *J. Am. Chem. Soc.* **2002**, *124*, 15006.
[35] A. J. Kirby, *Adv. Phys. Org. Chem.* **1981**, *17*, 183.
[36] R. P. Bell, A. D. Covington, *J. Chem. Soc. Perkin 2* **1975**, 1343.
[37] S. Scheiner, *Adv. Biophys. Chem.* **1993**, *3*, 119.
[38] D. H. Ess, S. E. Wheeler, R. G. Iafe, L. Xu, N. Celebi-Olcum, K. N. Houk, *Angew. Chem.* **2008**, *120*, 7704; *Angew. Chem. Int. Ed.* **2008**, *47*, 7592.
[39] B. Carpenter, *Angew. Chem.* **1998**, *110*, 3532; *Angew. Chem. Int. Ed.* **1998**, *37*, 3340.
[40] For a thorough discussion of time-dependence in catalysis, see G. F. Sweigers, *Mechanical Catalysis*, Wiley, New York, **2008**.
[41] B. J. Spencer, A. H. Zewail, *ChemPhysChem* **2005**, *6*, 2261.
[42] J. S. Feenstra, S. T. Park, A. H. Zewail, *J. Chem. Phys.* **2005**, *123*, 221104.

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