

# Chemical reactivity in organized media: statistical entropy and information in crystals and enzymes

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The control of chemical reactivity has been a subject of intense research activity for many years. It is known that supramolecular systems are capable of influencing the outcome of chemical reactions to levels not easily achieved by homogeneous liquids. Their influence is not always expressed through specific interactions that stabilize a transition state. Their role can be frequently ascribed to the structural pre-organization of the reactant towards particular chemical reactions. Because of this, systems as diverse as micelles, zeolites, enzymes and crystals are frequently referred to as organized media. Recent work on reactions in crystalline solids and enzymes suggests that reactions in organized media may be analyzed with an intuitive model based on simple statistical entropy principles.

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## Introduction

Organized media is a term used to describe a wide variety of natural and artificial supramolecular systems [1]. Organized media may vary widely in chemical composition, architecture, order and dynamics. A small set illustrating this variety may include enzymes, monolayers, membranes, host-guest compounds, polymers, DNA, zeolites and molecular crystals [2]. Reactions in organized media occur under superstructural and dynamic influences that are more complex than those in homogeneous solution or in the gas phase. Although some systems are acid-base or redox active, the term organized media stresses a role that may be considered chemically passive. Terms such as chelate effect [3], passive template effect [4], supramolecular assistance to molecular synthesis [5], molecular traffic control [6], percolation in porous networks [7] and topochemistry [8] illustrate the role of organization on reactivity. This organization is exerted mainly by mediating the encounters, conformational preferences, distances and orientations required along specific reaction trajectories.

## Reactions in crystalline solids

The crystalline solid state is the most rigid and highly organized medium of all. Crystalline solids also offer the highest degree of structural information when analyzed by single crystal X-ray diffraction, polarized spectroscopy and magnetic resonance. While it has been shown that reactions in crystals may occur with both control and yields not

achievable by any other medium (with the exception of enzymes) [9–11], their chemistry remains counterintuitive. Although some interesting reactions in crystals have been discovered by serendipity, there has been a great deal of systematic research activity in the area. The extraordinary nature of reactions in crystals has been illustrated with examples that include the formation of products that are never observed in solution, the generation of optically active products from achiral reagents, the formation of single crystalline polymers and the kinetic trapping of highly reactive intermediates [12–14]. The potential of crystal chemistry for mechanistic studies, solvent free synthesis and materials applications is now fully recognized. In this article chemical reactivity in organized media will be reviewed with a view that may help us to understand crystal chemistry in a general and intuitive context.

## Understanding and exploiting complexity

A general quality that is common to all organized media is their superstructural and dynamic complexity. Reaction rates and product selectivities reflect conditions that are different from those encountered in homogeneous media. Reactivity models and kinetic analyses developed for reactions in gases and liquids do not apply and qualitative explanations with limited predictive power must be offered. As various levels of complexity are recognized in different systems, such as phase transfer catalysis, hydrocarbon cracking by zeolites, conductivity in TTF (tetrathiofulvene) salts, solid supported reactions, enzymatic catalysis, nonlinear optical materials and so on, it is clear that complexity can be advantageous and beneficial.

The two most important motivations behind studies on chemical reactivity in organized media come from: firstly, the search for a better understanding of chemical reactivity in very complex systems; and secondly, the potential offered by exploitation of their catalytic effects. Although research in these areas overlaps extensively, there is some emphasis on the use of photochemical probes for the former and synthetic chemistry in the latter.

## Photochemical probes

The rapid dynamics of association–dissociation, sorption–desorption, escapes–encounters, conformational motions, and the need to have only small perturbations at constant temperatures, have led to the use of photochemical and photophysical probes as the preferred approach to explore organized media [15]. Photochemical probes with nano- to millisecond resolution and careful experimental design continue to be implemented to document increasing levels of complexity in association–dissociation phenomena [16]. In the reactions of crystals, photochemical excitation enables nonintrusive activation at temperatures that are well below

the melting point of the material [17], and for studies at temperatures near zero Kelvin in order to investigate quantum mechanical tunneling [18,19].

### Synthetic enzymes

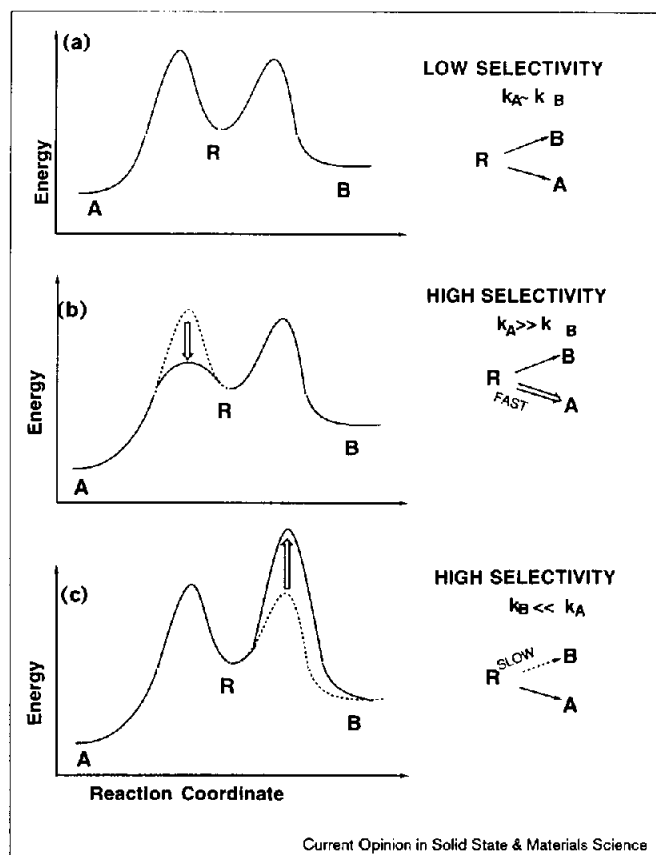
In addition to recent developments in the area of catalytic antibodies [20,21] and spectacular advances in enzyme modifications by using the tools of molecular biology [22], research explicitly aimed at the development of artificial enzymes has centered on the synthesis of modified hosts. These include modified cyclodextrins [3,23], cleft receptors [4,24], cyclophane hosts [25,26], macrocyclic polyamines [27] and several others [28]. As with natural enzymes, the specific interactions promoting or stabilizing the transition state are mediated by binding. However, while the structure of natural enzymes has been fully optimized by nature for efficient substrate binding, transition state stabilization and product release, the structure of most artificial enzymes still has room for improvement. It is expected that progress in the design of artificial enzymes will parallel progress in our understanding of weak intermolecular interactions. Indeed, it is interesting to note that the best results to date in the preparation of artificial enzyme-like systems comes from organometallic chemistry, with a powerful combination of well-established ligand synthesis, ligand-to-metal binding, and relatively well understood transition metal acid-base and redox chemistry [29–31]

### Selectivity

The catalytic activity exerted by enzymes is the greatest challenge to our understanding of chemical reactivity in organized media. It is recognized that the selectivity and specificity exerted by enzymes comes from their ability to reorganize the rates of prospective reactions as compared to those observed in homogeneous solution. Wolfenden and co-workers [32–34] have shown that enzymatic reactions may display rate accelerations of the order of  $10^{17} \text{ s}^{-1}$ . Effects like this indicate that the free energy of activation of the catalyzed reaction must be much lower than that of the uncatalyzed one. In terms of selectivity, a reactant, R which would normally give two products both A and B (Figure 1a), will react selectively if one of the two pathways can be accelerated (Figure 1b). A less appreciated (and sometimes controversial [35,36]) scenario that can also result in very high selectivity occurs when one reaction pathway is decelerated relative to the others by increasing its activation free energy (Figure 1c) [37].

It is expected that organized media may affect the selectivity of chemical reactions not only by rate acceleration but also by slowing down the rates of competing processes. To control the selectivity from a given substrate one needs to know how to change the rate constants of certain pathways in a selective manner. Strategies to do this based on linear free energy relations, solvent effects, steric effects, substituent effects and so on have been investigated over the years. Although these studies have increased our understanding of reaction mechanisms, selective changes

Figure 1



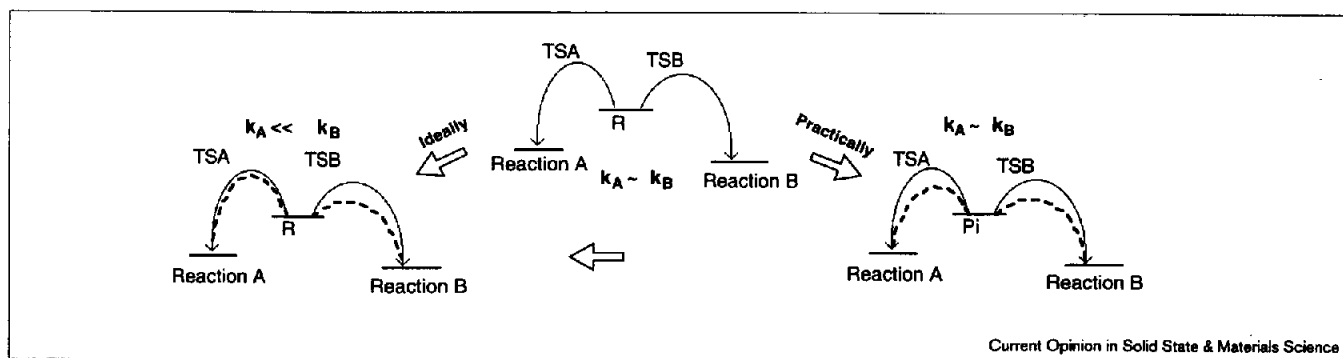
Reaction profiles for chemical reactions that occur (a) with low product selectivity, and strategies for increasing product selectivity by (b) accelerating desirable reactions or, (c) by slowing down undesirable pathways. A and B are products;  $k_A$  and  $k_B$  represent rate constants of reactions A and B, respectively; R, reactant.

in the activation energies of competing pathways are difficult to accomplish. Rather than accelerating or decelerating a specific reaction (Figure 2, left), most perturbations lower or rise the energy of all transition states in a similar manner (Figure 2, right). Furthermore, attempts at controlling chemical reactivity and selectivity by changing activation energies suffer from the exponential dependence of the rate constant on the activation energy. Small changes in activation energies may result in very large variations in rate constant values. Manipulating rates and selectivities by changing activation energies in solution can be thought of as a low resolution approach to controlling chemical reactivity.

### From enzymes to organized media

With the unsurpassed performances found in nature, physical organic chemists have turned to models of enzymatic catalysis for inspiration and clues [38–42]. Effects such as proximity, effective molarity, orbital steering, and desolvation have been analyzed along with specific interactions that stabilize the transition state. Although some debate continues on how to factorize contributions from enthalpic

Figure 2



Enthalpic perturbations of competing reactions tend to affect competing processes in a similar fashion.  $k_A$  and  $k_B$  represent rate constants of reactions A and B, respectively;  $P_i$ , state of reactant (R); TSA and TSB are transition states of A and B, respectively.

and entropic factors to rate acceleration [41,42], our understanding of enzymatic activity has increased during the last few years. Organized media, such as enzymes, may have a deep effect on chemical reactions by affecting their 'rate limiting step'. An enzyme-substrate complex (the formation of which may become rate limiting itself) may affect a (formerly) elementary reaction not only by altering the activation energy term,  $E_a^\ddagger$  of a general rate expression,  $k = A \exp(-E_a^\ddagger/RT)$ , but also by reorganizing the entropy of the reacting system. Superficially, the physical meaning of  $E_a$  seems clearer than that of the pre-exponential factor  $A$ . The former is defined as the enthalpy difference between the transition state and the reactants and, in principle, it may be calculated with great accuracy. The frequency of encounters, orientational effects, conformational demands, molecular organization and the overall likelihood of transition state formation are associated with the pre-exponential term 'A' of the rate equation. Collision theory considers  $A$  to be a sterically-scaled frequency factor and the Arrhenius equation uses it as a temperature-independent empirical frequency parameter. Transition state theory formulates  $A$  in terms of the partition function of the transition state, or the difference in entropy between the transition state and the reactants. Although these interpretations from gas phase kinetics support an intuitive notion that links the pre-exponential factor,  $A$  with organization and order, it may be convenient to reformulate the problem in condensed media to allow for rate limiting diffusion, binding, molecular rotations, conformational changes, and so on.

### Statistical entropy, information and the amount of choice

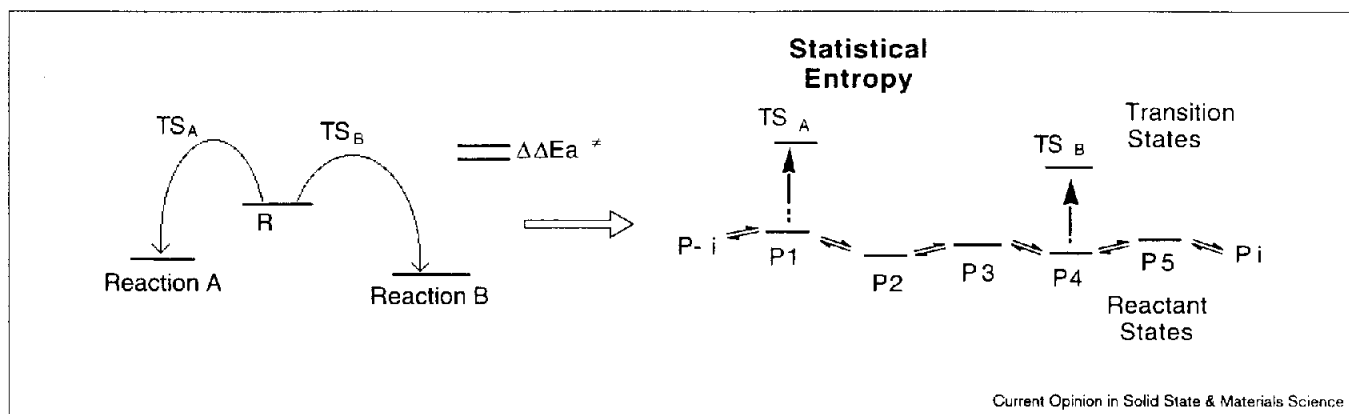
An intuitive, simple and general model that helps analyze reactivity in organized media can be based on statistical entropy [43]. In solid state work by the group of the author this model has been used as a general starting point to analyze results and design experiments. In this model, the effect of the medium on the population of the ground state conformations, vibrations, rotations, collisions and spin states that influence the reactivity of the reactant is

considered. A close link between statistical entropy and Shannon's information theory gives a satisfying connection between organization, complexity, the amount of choice, or the amount of information needed to describe a given system [44].

A schematic representation illustrating the use of statistical entropy in chemically reacting systems is given in Figure 3, where it is explicitly recognized that a reactant,  $R$  may exist in a wide variety of states,  $P_1, P_2, \dots, P_i$  [43,45]. The mathematical relationship between statistical entropy,  $S$  and the population fraction,  $X_i$  of states,  $P_i$  is given by  $S = -S \sum X_i \log X_i$ . The magnitude of the statistical entropy depends on the number of states and on their relative populations. As those populations are determined by the relative energies of states,  $P_i$  (using the Boltzmann equation), and because these energies are determined by their structures, statistical entropy can be used as a measure of the amount of information or the amount of choice in a chemical system. Although a similar analysis with a different definition of  $P_i$  can be used to analyze molecular properties, the  $P_i$  in Figure 3 represent the states of a molecular ensemble. A large value of  $S$  describes a large number of evenly occupied states (high information content and large amount of choice), whereas a small value indicates that only a few states are occupied (low information content and low choice; it should be noted that Shannon's definition of information content may be counter intuitive. The more information, the more choices there are and the less one knows about the system). Statistical entropy is directly related to the homogeneity of a system. A nearly perfect crystal near zero Kelvin has a very low statistical entropy because all the molecules in the sample are restricted to a limited number of states. In contrast, a sample in the gas phase, where molecules may occupy a large number of states defined as translational, rotational, vibrational, collisional, and so on, has a very large statistical entropy.

Although the effect of organized media on statistical entropy will be very complex (and perhaps rigorously

Figure 3



Schematic representation of statistical entropy in a chemical reaction by disclosure of the reaction profile along the states of the reactant.  $E_a^\ddagger$ , activation energy; R, reactant.

untractable), information theory suggest that not all complexity needs to be relevant to the outcome of a chemical reaction. If a chemical system is considered to be an information source (with  $P_i$  states or words), and a reaction trajectory is considered to be a communication channel, then the final product may correspond to the receiver (Figure 4). One can recognize that product formation may be thought of as a fine-tuned receiver and that not all the states in the system (words) will contain readable structures (messages). It is also important and valuable to recognize that, at a first approximation, statistical entropy can be factorized to consider only the states that are pertinent to the chemical reaction. For instance, the analysis of bimolecular reactions in condensed media can start by considering states defined by diffusion and solvent cages. Cyclization reactions can be analyzed in terms of conformational states. A biradical cyclization competing with trapping by scavengers may be formulated in terms of collisional, conformational and spin states. Not all information is readable by all receivers and not everything in a transmission is relevant to the message. For instance, chemical dynamics is probably irrelevant to radioactive decay just as the font and ink used to print this review do not make or change any of its meaning.

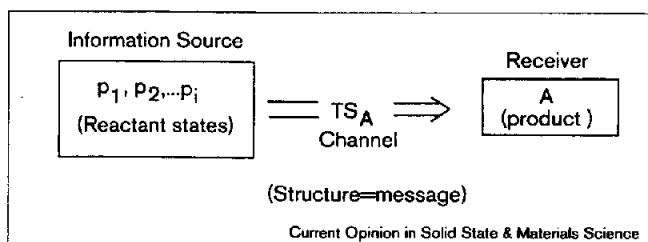
It is expected that organized media will redistribute gas phase energies and create a new ensemble with a large number of states  $P_i'$ . The new states will be supramolecular in nature [1], they may be very short-lived, and their structures will be determined by noncovalent interactions. Homogeneous media will limit reactant molecules within a more confined subset of  $P_i$  (low entropy) whereas heterogeneous systems will give rise to a much greater variety of states and a higher statistical entropy.

The significance of statistical entropy and information theory to chemical reactivity is further illustrated in Figure 3. A disclosure of the reaction coordinate along the

reactant surface shows that reactions A and B must occur through transition states  $TS_A$  and  $TS_B$ , respectively. As these correlate with the reactant states  $P_1$  and  $P_4$ , reactions A and B reflect the probability of finding the reactant in states  $P_1$  and  $P_4$ , respectively. A simple illustration can be given by using an analogy between a set of states,  $P_i$  and the words given by a three letter information source. For instance, not all combinations of the letters Y, E and S will have a meaning in the English language. Out of all six possible three letter combinations (states or words), only the word YES has meaning to a receiver that is fluent in English. Similarly, a chemical system may have a large number of states but only few will have meaning in terms of chemical reactivity. Many messages may be contained in the information source which will be meaningful to different receivers. For instance the word given by the letters SYE may have meaning for someone who speaks another language. This brief analysis suggests that structural, spectral and functional messages contained in a chemical system must be deciphered by the proper 'receiver'. This also suggests that information (or entropy) without a context may have limited significance.

With the above analogy, one may see that reactions that occur from ground states that are scarcely populated, like rare words, will occur with a frequency that is limited by the information source (diffusion controlled). Reactions that occur from states that are well represented because of favorable energies will occur with frequencies limited by the capacity of the channel (activation control). As state populations are temperature dependent, information at this level will appear in the activation energy term of the rate equation. In contrast, the elementary reaction from a 'readable' reactant state to the products should be part of the pre-exponential term. This suggests that activation enthalpy is used to prepare the reactant whereas activation entropy relates to the passage through the transition state from a suitable ground state structure to the final product. The significance

Figure 4



Idealized analogy between the elements of a chemical reaction and the elements considered in information theory.  $TS_A$ , transition state.

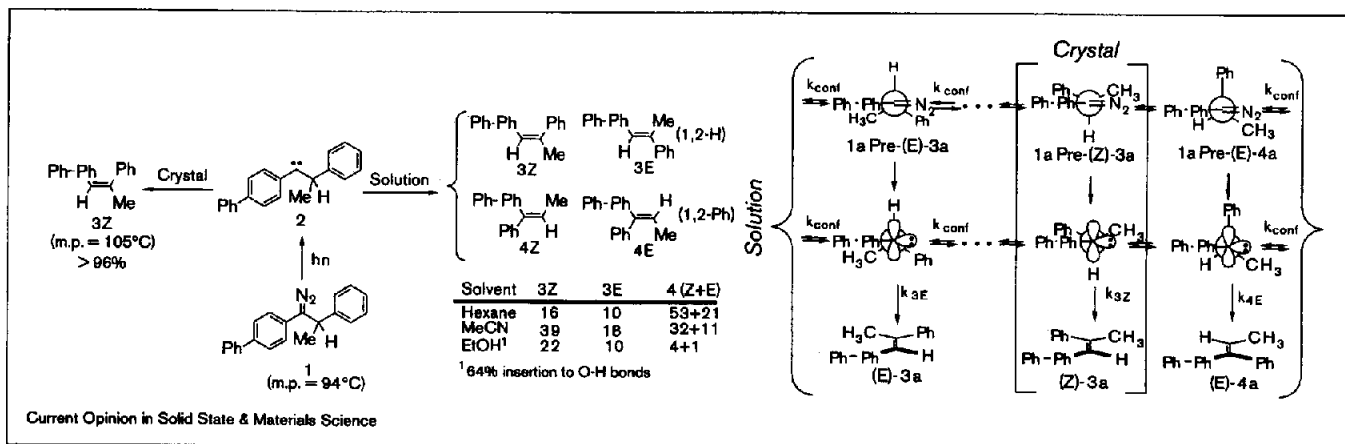
of this analysis is that ground state conformational motions, collisions, and so on, can be considered elementary steps of a complex reaction. Therefore, a mechanism by which organized media can accelerate or decelerate a reaction is by changing the ground state populations (i.e. changes at the information source). The use of enthalpy from favorable binding interactions to decrease the statistical entropy of the system at a given temperature is analogous to a phase transition and indicates how one may analyze the relation between the enthalpic and entropic components in a chemical reaction. In a crystalline solid, packing interactions freeze the equilibrium shown in Figure 3 and reduce the statistical entropy of the system. If reactant R crystallizes into state  $P_2$ , no reaction will ever be observed below melting. The rate limiting step will be the destruction of the crystal lattice to allow for the population of  $P_1$  and  $P_4$ . On the other hand, if reactant R crystallizes into state  $P_1$  one will expect highly selective formation of product A and perhaps an accelerated chemical reaction. Organized media may reduce the overall enthalpic requirement of the gas phase reaction by ordering the structure (or superstructure) of the reactant closer to that required for the elementary

reaction. Pursuing this analogy further, it is expected that organized media can also affect the capacity of the channel by setting up properly oriented charges, acids/bases, electron donors, vibrational modes, and so on, to facilitate passage through the (supramolecular) transition state.

Strategies for controlling specificity and selectivity are explicit within the statistical entropy model and depend firstly on ground state selection and secondly on transition state stabilization. One may safely speculate that enzyme proficiency is likely to occur not only by favoring a particular ground state but also by reducing the energy difference between ground and transition states. It is interesting to note that a view based on statistical entropy suggests that reaction rates may be controlled by organized media over the entire range of the pre-exponential factor. This means that reaction rates might be controllable at any given temperature (as long as organized media can exist), between zero and the maximum allowed by transition state theory for the elementary reaction (i.e. up to  $10^{14} \text{ s}^{-1}$ ).

An example illustrating the above model with a reaction in a crystalline solid was recently published by Shin *et al.* [9,46] It was shown that molecular crystals are capable of controlling the reactivity of carbenes to unprecedented levels by selecting one out of several conformational states of a diazo precursor (Figure 5). The reaction involves a photoinitiated steady state decomposition of a diazo compound in its own crystalline lattice. In solution, carbenes generated upon extrusion of  $\text{N}_2$  have very short lifetimes because they react rapidly. Insertion to the solvent, addition to double bonds, dimerization, and intramolecular 1,2-R migrations occur very rapidly. In a crystalline solid, bimolecular reactions are generally prevented. Unfavorable alignment between prospective reaction centers and the absence of solvent constitute a selection of

Figure 5



Excellent control of challenging carbene reactivity by crystals as an example of a chemical system with low statistical entropy and a precise chemical message.

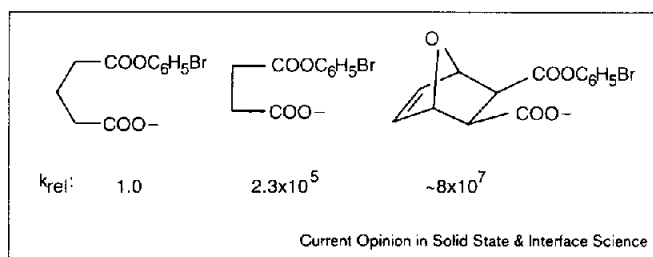
collisional states. The unimolecular reactions of carbenes are stereoelectronically demanding and conformationally dependent. The conformational states that are pertinent to these reactions are those that define the alignment of the migrating group with the empty p-orbital of the carbene in the singlet state (Figure 5, right). Although all conformational states are well represented in solution (high statistical entropy), there is only one conformational state present in the crystal (low statistical entropy). The analogy between Figure 3 and the right part of Figure 5 is evident as the selectivity of the reaction is given by the structural information present in the crystal of the reactant.

The statistical entropy model can be also applied to the effect of molecular structure on chemical reactivity. Lightstone and Bruice [41,42] recently analyzed the conformational space of a series of substituted glutarates, succinates and 3,6-endoexo-D<sup>4</sup>-tetrahydrophthalate monoester esters, which are commonly used to illustrate proximity effects. The monoesters cyclize with rates that vary over 7 orders of magnitude depending on the structure to give anhydrides. Three representative examples of the anhydrides are shown in Figure 6. After a complete stochastic conformational search for each compound, Lightstone and Bruice [41,42] analyzed their results in terms of two subsets of conformers: a set of reactive, or near approach conformers (NAC), and the remainder nonreactive ones [41,42]. An excellent correlation was observed between the known rate constants and the Boltzman probabilities of the reactive conformers. It was also shown that activation free energies correlate better with the enthalpy difference between the most stable ground state and the lowest energy NAC, than with the entropy output from the molecular mechanics program MM3. Their results attest the importance of populating the reactive states and confirm that the temperature dependence of the rate equation should be related to changes in state populations. Their results also showed that the activation enthalpy becomes very small when the energetic price for populating the reactive state is covered by molecular constraints. The lack of correlation with the calculated entropy supports our suggestion that only some contributions to the total entropy are pertinent to the reaction: that is, not all information contains readable messages. The above examples suggest that besides crystals, enzymes, and molecular constraints, one may use hydrophobic forces, binding interactions, adsorption, crystallization, and so on, to pre-organize the reactant in a ground state that correlates with the transition state of a desirable transformation.

### Perspectives in crystal chemistry

Despite a number of advantages cited in the introduction, there are some limitations to chemical reactions in the crystalline solid state and much work remains to be done. To this date, reactions in crystals still have little predictive power. This problem will be solved in the near future as more robust reactivity models, techniques and a larger data base become available. There has been a great deal of

Figure 6



Representative examples of monoesters studied by Lightstone and Bruice [41, 42] along with their corresponding cyclization rates ( $k_{rel}$ ).

progress in the area of crystal engineering [47]. 'Designer' crystals with a controlled number of components with desirable distances and orientations may be available in the near future. Following pioneering studies on the 2p+2p dimerization of alkenes and several polymerization studies by workers in the mid 1960s and early 1970s, Scheffer and co-workers [48–50] have demonstrated that unimolecular rearrangements offer a reliable strategy to bypass the need for specific packing arrangements. McBride and his co-workers [51,52] have shown extremely detailed and precise reaction mechanisms in several crystalline systems. Toda and co-workers [13] have exploited crystalline host-guest complexes, and have demonstrated several reactions that occur upon the mechanical mixing of two different solids. There are also important efforts by several workers to develop and exploit two-component crystals. Some strategies include salt formation from carboxylic acids and amine bases [53], ground-state charge transfer complexes [54], and two-component hydrogen-bonding complexes [55,56]. The group of the present author has shown that reactions in crystals may be carried out, analyzed and exploited in a reliable and systematic fashion by using highly reactive intermediates [8–11,46,57]. One of the most important sources of complexity in solid state reactions arises from the fact that product formation perturbs the crystal lattice responsible for the selectivity that is observed there in the first place. The accumulation of product in the crystals of the reactant makes solid state reactivity a challenging nonlinear problem. This is reflected in kinetic analysis which give rise to rate constants following complex laws. Recent analysis guided by views that address reactions in crystals from the point of view of phase continuity and phase separation suggest that clean, selective and quantitative solid-to-solid reactions will be more common than previously anticipated [17].

### Conclusions

Chemical reactions in organized media have challenged chemists for a long time. The importance of understanding and exploiting complexity will guide the development and refinement of reactivity models that will help us take advantage of supramolecular systems. Statistical entropy provides an intuitive approach to specificity and selectivity and hints to meaningful ways of factoring and relating enthalpic and entropic factors.

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