

# Engineering Carbene Rearrangements in Crystals: From Molecular Information to Solid-State Reactivity

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## ABSTRACT

Although severely restricted, reactions in crystals have delivered some of the most impressive examples of chemical control and provided an ideal medium for detailed mechanistic studies. However, to take full advantage of their potential and avoid their shortcomings, a systematic approach for the reliable design of reaction in crystals is required. To that end, strategies based on structural and energetic information contained at the molecular level have been explored with reactions involving carbene rearrangements.

## Introduction

The milestones in organic chemistry involving reactions in the solid state are remarkable but seldom appreciated (Scheme 1). Examples range from the “birth” of organic chemistry in 1828<sup>1,2</sup> to microlithography, the chemical process that propelled society into the information age by providing the technology needed to make powerful computers.<sup>3</sup> Other examples of practical and historic interest include the degradation and formulation of pharmaceuticals solids,<sup>4–6</sup> the characterization of molecules with high spin states,<sup>7</sup> the prebiotic generation of optical activity,<sup>8–10</sup> and the synthesis of  $\pi$ -conjugated polymers.<sup>11</sup>

Given the potential illustrated by the examples in Scheme 1 and many others not included,<sup>12</sup> the lack of systematic knowledge in solid-state organic chemistry in the 21st century is alarming. Mainstream academic chemistry has perceived it as esoteric, and industrial chemists have approached it empirically. Fortunately, developments in structural chemistry, rate theory, analytical methods, and computational techniques are rapidly transforming these perceptions.

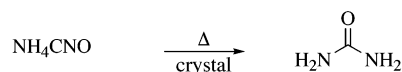
## The Topochemical Postulate: A General Theory with Limited Predictive Power

The most important limitation in solid-state organic chemistry is the lack of predictive power. Learning how

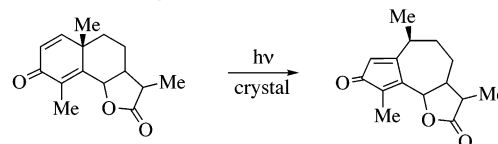
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## Scheme 1. Milestones in Solid-State Organic Chemistry

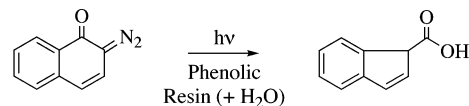
Wholer 1828: First “organic” compound synthesized



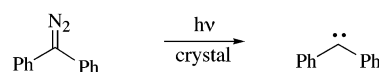
Pfizer 1849: First drug formulated in the US



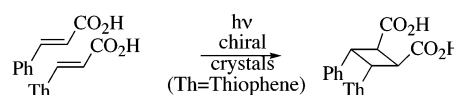
Süs 1949: First and most used microlithographic system



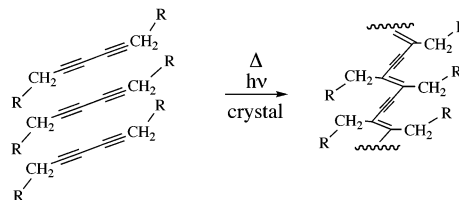
Murray et al. 1962: First triplet molecule observed



Schmidt et al. 1971: “Spontaneous” generation of optical activity



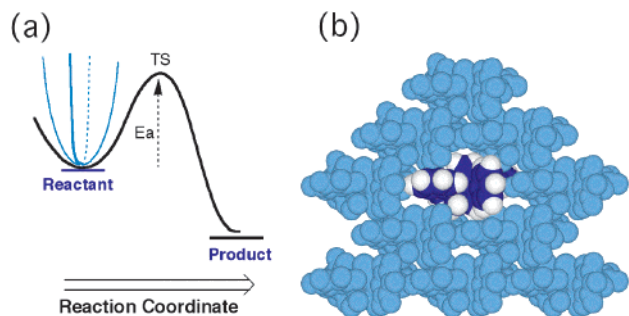
Wegner et al. 1971: Single crystalline conducting polymers



to engineer reactions in crystals will help establish the rules needed to exploit their potential and avoid their shortcomings. Wishing to learn whether the rational design of reactions in crystals is possible, we have searched for intuitive models to guide us in the selection of reliable reactions and suitable substrates. Until recently, the only model that could help accomplish this was the topochemical postulate. Proposed by Kohlshutter in 1918<sup>13</sup> and refined by Schmidt and co-workers in the 1960s,<sup>14</sup> it states that reactions in crystals occur with minimum atomic and molecular motion. Qualitatively, the postulate implies that reactants, transition states, and final products must fit within a “reaction cavity” formed by their close-packed nearest neighbors.<sup>14b</sup> Quantitatively, chemists report whether a reaction occurs under topochemically “allowed” distances determined empirically from studies with analogous compounds.<sup>15</sup>

Unfortunately, the topochemical postulate gives limited guidance and predictive power. Suitable intermolecular distances do not guarantee that a reaction will occur,<sup>16</sup> and seemingly forbidding packing structures do not always

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**FIGURE 1.** (a) A gas-phase reaction coordinate with a blue parabola representing the nonbonding crystal potential generated by interactions with neighboring molecules in the crystal. (b) A small portion of a crystal illustrating a reactant surrounded by its close neighbors.

result in stable solids.<sup>17</sup> As a counterpart of the topochemical postulate and other descriptive concepts, Eckhardt and Luty proposed a rigorous quantitative theory of reactions in crystals based on elastic multipoles.<sup>18</sup> Their model considers molecular (local) and environmental (global) forces involved in chemical reactions. Although part of our analysis coincides broadly with their theory, we will focus on qualitative views that may help identify and design potential solid-state reactions.

## Engineering Reactions in Crystals

To engineer reactive crystals, one needs to consider restrictions on (1) the number of components, (2) the magnitude of the activation barriers that can be overcome at temperatures that are compatible with the existence of crystalline phases, and (3) the limited structural changes allowed within a solid. In the sections that follow, we will analyze the molecularity, energetics, and information content of crystals with the aim of selecting the most promising reaction types and predicting their outcome.

## Molecularity

Elementary reactions in crystals can be unimolecular or bimolecular. Since most crystals are pure substances, most bimolecular reactions occur between identical partners.<sup>19</sup> The main challenge in bimolecular reactions is that they require precise distances and orientations between potential reaction centers. In contrast, unimolecular reactions rely less on specific packing structures and more on conformational factors. Since it is difficult to predict packing motifs for bimolecular reactions in a reliable manner,<sup>20</sup> our early efforts have been focused on unimolecular processes.

## Energetics of Reactions in Crystals

The topochemical postulate gives necessary but insufficient guidelines to predict reactions in crystals. Recognizing that reactions must occur with severely limited kinetic energy, we have explored an energetic viewpoint that considers how gas-phase reaction coordinates can be modified in a crystal lattice (Figure 1). We recall that transition-state theory derives from a hypothetical equilibrium ( $K^\ddagger$ ) between reactant (R) and transition state (TS) and a rate constant ( $k^\ddagger$ ) that expresses passage to the product (eq 1):<sup>21</sup>

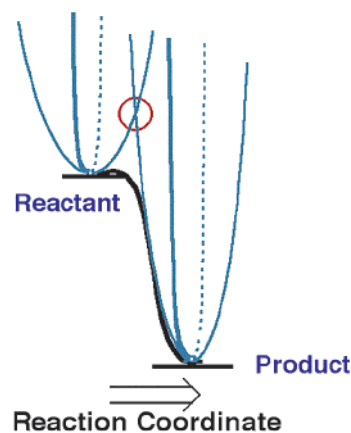


With reference to Figure 1, the structure of the reactant in the gas-phase oscillates about its energy minimum given by the lowest point of its energy surface. Increasing amounts of heat cause larger amplitude oscillations that populate higher translational, rotational, and vibrational states.<sup>21</sup> As the reactant explores an increasingly larger portion of its energy surface, more molecules approach the transition state. Statistical theories can be used to calculate the value of  $K^\ddagger$  in solution and in the gas phase, and the rate constant  $k^\ddagger$  is identified with the period of a single vibration.

Confined by close neighbors, reactants in crystals can explore only a modest portion of the surface accessible in liquid or in gases (Figure 1b). This is illustrated with a simple parabolic potential representing the nonbonding interactions between a reacting molecule and its close neighbors. As these forces prevent molecules in crystals from undergoing large amplitude motions, most of their thermal (kinetic) energy is distributed over a large number of lattice vibrations.<sup>22</sup> It is clear from Figure 1 that most reactants in crystals will be unable to approach the transition state, giving  $K^\ddagger = 0$ , unless the crystal potential (shown in blue) is destroyed by melting or subliming.

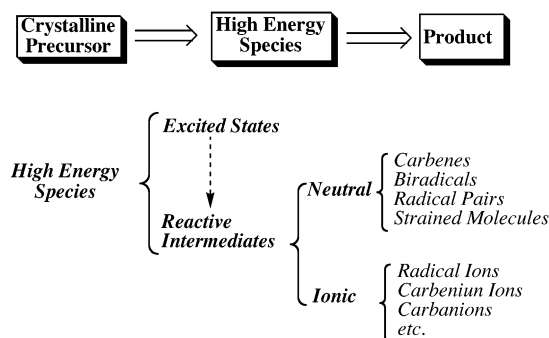
Having recognized that reactions in crystals can only occur with restricted forms of kinetic energy, the most promising alternatives will be given by reactants with a high potential energy content (Figure 2), or by reactions that occur by quantum mechanical tunneling. Although we have analyzed examples of solid-state reactions in both categories,<sup>23,24</sup> here we will focus our analysis on reactions involving high energy species.

**A. Reactants with High Energy Content.** Molecules with sufficiently high energy content can break weak bonds to make new stronger ones, even under conditions of limited translational and rotational energy. As suggested



**FIGURE 2.** Representation of the nonbonding potential of a crystal host (with blue parabolas) for reactant and the product structures superimposed on a highly exothermic gas-phase reaction (black line). The barrier for the solid-state reaction is indicated with a red circle.

Scheme 2. From Stable Crystals to Products through High-Energy Species



by the Hammond postulate, low-energy and reactant-like transition states are expected to facilitate reactions that can only occur with small structural changes. Considering the influence of crystal potentials on reactant and product structures (blue parabolas in Figure 2), one may expect barriers that have contributions from the intrinsic gas phase transition state and from steric interactions with the environment. The analogy between Figure 2 and the model proposed by Marcus to formulate electron transfer theory is striking. The feasibility and efficiency of both reaction types can be strongly influenced by the environment.<sup>18,25</sup> A computational approach to document this model investigated in our group will be described below.<sup>26</sup>

**B. High-Energy Species.** Excited states and reactive intermediates with energy surfaces such as that in Figure 2 should be available from a large number of stable crystalline precursors. High-energy species may be generated thermally or photochemically and may be neutral or ionic (Scheme 2). Radical pairs, biradicals, carbenes, nitrenes, strained molecules, and radical ions are among the possible intermediates. Here we will describe our work on the generation and study of carbenes in crystals.

**C. Carbene Reactions in Crystals.** Carbenes are unusual molecules with divalent carbon, which should satisfy the conditions illustrated in Figure 2. Studies describing the generation of carbenes in solids date back to the 1960s, when diphenyl carbene was characterized by Trozzolo and co-workers as the first molecule with a triplet ground state (Scheme 1).<sup>7</sup> The first detailed reaction of a carbene in a crystalline solid was studied shortly after by Doetschman and Hutchison.<sup>27</sup> They showed that additions of diphenyl carbene to 1,1-diphenylethylene and diphenyldiazomethane are topochemically controlled (Figure 3).

**D. Intramolecular Reactions of 1,2-Diphenylalkylidenes.** For a systematic study of carbene reactivity in crystalline solids, we chose a set of aryl-alkylcarbenes derived from 1,2-diaryldiazoalkanes (Scheme 3).<sup>28</sup> Although compound **4a** will be analyzed in detail, analogous results have been obtained with similar compounds.<sup>29</sup> Crystals of **4a** (mp = 94 °C) are stable for months at ambient temperature but react rapidly upon photochemical excitation.<sup>30</sup> Solution studies with **4a** and other 1,2-diphenylethylidenes confirmed their exceedingly high reactivity. Product mixtures included alkenes **5aZ** and **5aE** from 1,2-H shifts, **6aZ** and **6aE** from 1,2-Ph migrations,

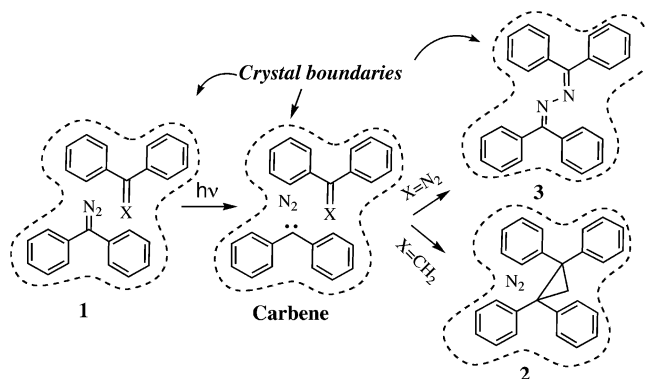
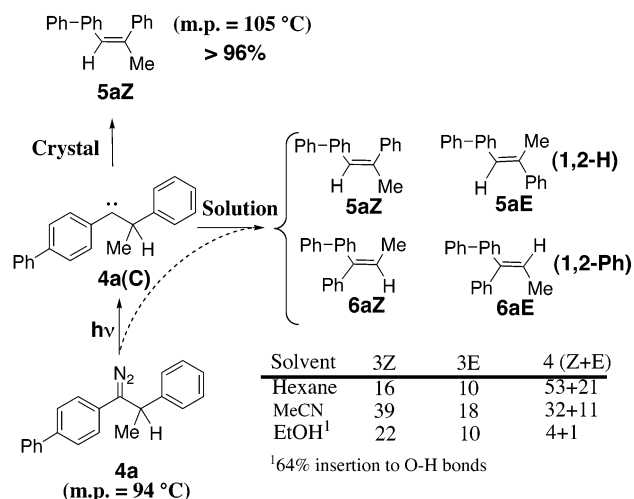


FIGURE 3. Addition of diphenyl carbene to 1,1-diphenylethylene (X=CH<sub>2</sub>) and diphenyldiazomethane (X=N<sub>2</sub>) gives tetraphenyl cyclopropane **2** and benzophenone azine **3** in a mixed crystal of the alkene and diphenyldiazomethane.

Scheme 3. Generation and Reactivity of a Carbene Intermediate in the Solution and Crystal-Phase Reactions of a 1,2-Diaryldiazoalkane

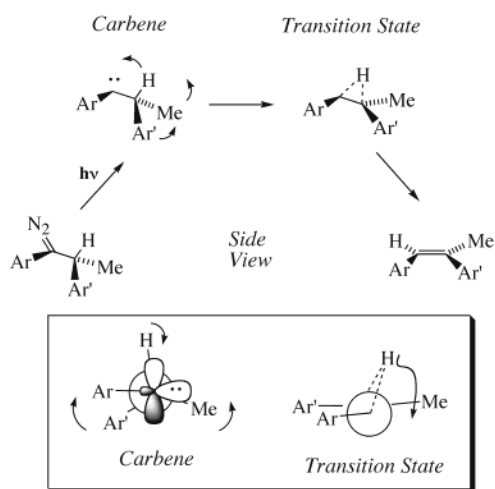


as well as reactions with solvents. Solution studies suggest that 1,2-Ph migrations in 1,2-diphenylethylidenes occur primarily in the triplet state while 1,2-H shifts are dominant in the singlet manifold.<sup>30b,31,32</sup> Product distributions are susceptible to changes in temperature and solvent,<sup>33</sup> and their chemistry is complicated by reactions from the diazo precursor that bypass the carbene (Scheme 3, dotted arrow).<sup>31</sup>

In contrast to their complex solution reactivity, crystals of diazo **4a** reacted remarkably cleanly.<sup>32</sup> Irradiation of **4a** with  $\lambda > 380$  nm proceeded to completion in a solid-to-solid reaction where the (*Z*)-isomer **5aZ** was the only product. While detection of **4a(C)** by EPR at 77 K revealed indefinitely long lifetimes, reactions in crystals near ambient temperature proceeded within a few seconds. Remarkably, the lifetime of the (presumably) spin-equilibrated carbene in solution at 298 K was only 50 ns,<sup>34</sup> revealing a remarkable 6–7 orders of magnitude difference between solution and crystals.

The remarkable deceleration of the crystal reaction may arise from changes in the rate of intersystem crossing from the ground-state triplet to the thermally activated singlet, changes in the rate of the 1,2-H shift in the singlet carbene, or both. To evaluate the influence of the crystal on

Scheme 4. The Reaction Trajectory of the 1,2-H Shift



reactivity and selectivity, we must consider the reaction mechanism. 1,2-H shifts are known to occur from conformations where the  $\sigma$  bond of the migrating group is parallel to the empty p-orbital in the singlet carbene (Scheme 4).<sup>35,36</sup> The transition state is characterized by displacement of the hydrogen across the developing double bond and by planarization of the  $\alpha$ -carbon.

X-ray analysis of diazo **4a** and (*Z*)-stilbene **5aZ** revealed molecular structures that are consistent with the proposed reaction mechanism (Figure 4). The conformation of **4a** in the crystal has the two aryl groups gauche and the migrating hydrogen nearly perpendicular to the plane of the diazo group. Changes required from reactant to product include (a) loss of nitrogen, (b) displacement of the migrating hydrogen from the  $\alpha$ -carbon to the carbene center, (c) rehybridization of the  $\alpha$ -carbon from  $sp^3$  to  $sp^2$ , and (d) changes in bond-lengths that correspond to the product structure. The structural similarities of **5aZ** and **4a** are consistent with a topochemical reaction where the two molecules tolerate each other in a common crystal lattice.

**E. Steric Energies in the Solid-State Reaction.** The solid-state reaction was modeled with a combined quantum mechanics–molecular mechanics (QM–MM) method to investigate the interaction energy of the reacting carbene with other molecules in the crystal.<sup>28,37</sup> An intrinsic reaction coordinate (IRC) was calculated in the gas phase with *ab initio* theory (RHF-3-21G), and the steric potential of the crystal lattice was modeled with molecular mechanics (AMBER force field). The reaction coordinate in Figure 5 is defined by the distance of the breaking C–H bond as the structure changes from carbene to alkene. Gas-phase energies on the right scale confirm the high energy of the carbene with respect to the product ( $\Delta E_{\text{rxn}} \approx -70$  kcal/mol). Although the transition-state energy obtained by the HF 3-21G\* method was higher than that obtained by a more reliable B3LYP/6-31G\* calculation, IRC structures were reasonably good and were used to simulate the solid-state reaction.

As expected for a highly exothermic process, the transition-state energy is low and occurs early in the

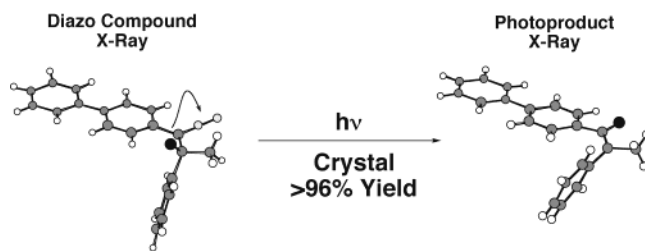


FIGURE 4. X-ray structures of diazo **4a** and (*Z*)-stilbene **5aZ** illustrating their structural similarities. The displacement of the migrating hydrogen, shown in black, is illustrated in the reactant structure with an arrow.

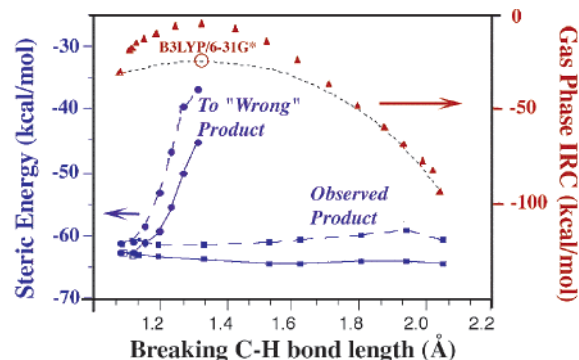
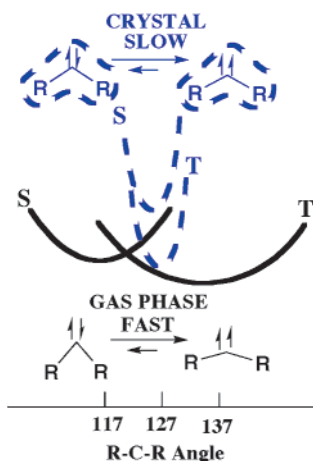


FIGURE 5. Gas-phase trajectory toward observed solid-state product (red triangles, scale on the right) and crystal trajectories for favored (blue squares) and disfavored (blue dots) paths (scale on the left). A correction to gas-phase RHF/3-21G activation energy with the B3LYP/6-31G\* method is indicated with a dotted line. Rigid-lattice calculations are shown with dashed blue lines and lattice-minimized calculations with solid blue lines. The reaction trajectory for the "wrong" product requires a conformational change in the crystal lattice prior to the 1,2-H shift (please see ref 26 for details).

reaction coordinate. The steric energies as a function of reaction progress for rigid and minimized crystal lattice calculations are indicated in blue color on the left scale (Figure 5). Consistent with the small atomic displacement suggested by the X-ray structures of **4a** and **5aZ** (Figure 4), the results in Figure 5 show a small intrinsic (gas phase) barrier and negligible steric repulsion in the solid state. Since formation of other products requires prior conformational changes, their formation was sterically forbidden within the same crystal lattice. A rapid increase in energy as a function of bond rotation toward alternative products is also illustrated in Figure 4 with the label "to wrong product".

The results in Figure 5 suggest that intrinsic and steric barriers for the singlet carbene are too small to account for the remarkable rate deceleration. Therefore, it is likely that the low reaction rate may be due to unfavorable populations of the singlet-state carbene. It is known that singlet–triplet energies are strongly affected by the magnitude of the R–C–R angle (Scheme 5).<sup>38</sup> Triplets tend to be linear and singlets bent.<sup>38a</sup> The gas-phase values for 1,2-diphenylethylidene, calculated with the UB3LYP/6-31G\* method, are 117° for the singlet and 137° for the triplet.<sup>39</sup> With an R–CN<sub>2</sub>–R angle of 126°, the structure of the precursor is in between. Hypothetical differences between the gas phase and crystal lattice potentials for

Scheme 5. Schematic Differences in the R–C–R Angle for Singlet and Triplet Carbenes



singlet and triplet carbenes are illustrated in Scheme 5. The gas-phase minima of  $117^\circ$  and  $137^\circ$  for the singlet and triplet states are likely to be distorted in the crystal to values that are close to  $126^\circ$ , as in the structure of the precursor. This strain may increase the magnitude of the singlet–triplet gap, slow the rates of intersystem crossing, and diminish the population of the singlet state. In fact, differences in triplet–triplet fluorescence of diarylcarbenes as a function of rigidity are a well-known manifestation of similar constraints.<sup>40</sup>

#### F. Product Accumulation and Lattice Relaxation.

Accumulation of product molecules lowers the melting point and causes disorder in reacting crystals.<sup>41</sup> Such structural perturbations can affect the selectivity in a significant manner.<sup>42</sup> However, some crystals have a remarkable tolerance for product accumulation. In the case of compound **4a**, high yields and good selectivities were observed upon excitation on the weak  $n,\pi^*$  transition at  $\lambda > 380$  nm.<sup>33,43</sup> Since product accumulation causes depression of the melting point, the phase diagram of reacting crystals should be analyzed to select a reaction temperature where no liquid phases can exist. Differential scanning calorimetric analysis (DSC) of **4a** showed that accumulation of **5aZ** occurs as a continuous solid solution with no liquid phases below  $60^\circ\text{C}$ .

Regarding the possible accumulation and dissipation of internal stress, a close analysis of the modeling studies described above suggested a possible dissipation mechanism. When we compared the structures of unreacted neighbors before and after the simulated reaction, we noticed that most molecules had experienced a significant degree of biphenyl twisting.<sup>44</sup> Experimental confirmation of this prediction was carried out by Raman spectroscopy by observing the appearance and growth of a characteristic band of twisted biphenyl at  $410\text{ cm}^{-1}$ <sup>45</sup> as a function of reaction progress (Figure 6). It is reasonable that soft conformational modes such as that may help relieve the stress that accompanies product accumulation facilitating solid-state reactions with high yield and selectivity.

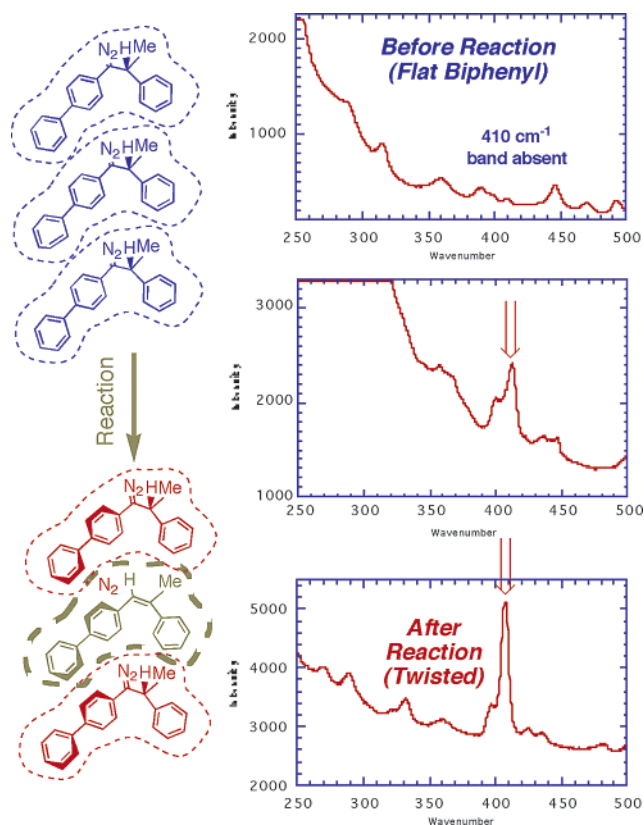


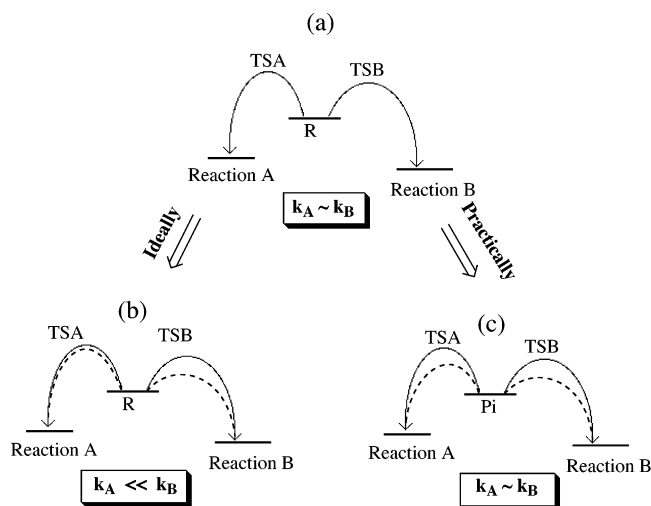
FIGURE 6. Raman spectra of crystals of **4a** before reaction and with increasing amounts of accumulated product (top to bottom). The band at  $410\text{ cm}^{-1}$  reveals twisting of the biphenyl group. Calculations suggest that flat biphenyl in unreacted starting material twists as a result of stress created by the product.

### Homogeneity and Order

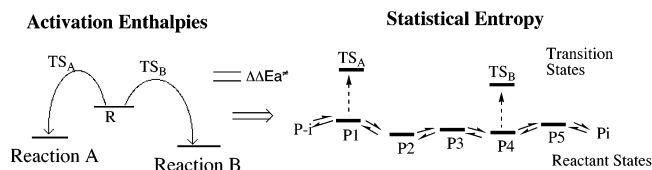
Crystals are highly homogeneous and remarkably ordered. For that reason, it is intuitively reasonable that chemical reactivity should be strongly influenced by entropic factors.<sup>46</sup> To analyze how entropy may affect the feasibility and selectivity of chemical reactions, we consider a reactant R with competing reactions A and B (Figure 7a). We assume similar transition states [ $E_a(\text{A}) \approx E_a(\text{B})$ ] and rate constants ( $k_A \approx k_B$ ) so that the selectivity of R is low.

To improve the selectivity of R, one may search for perturbations on the activation energies that make one reaction faster than the other. An ideal perturbation that favors reaction B ( $k_A \ll k_B$ ) is illustrated in Figure 7b. Unfortunately, the scenario for many reactions is less than ideal as most perturbations affect both barriers in a similar manner (Figure 7c). Knowing that crystals can control competing pathways with high efficiency, an intuitive model of their function would be highly desirable.

**A. Statistical Entropy and Information Content.** While most crystals are stable, a few contain information leading to remarkable chemical reactions. To describe the effects of crystals on reactivity and selectivity, one must consider the presence of reactive conformers, spin states, vibrational modes, lattice phonons, close neighbors, etc., as described by their statistical entropies. We have proposed that a close link between statistical entropy and information theory<sup>47,48</sup> provides an intuitive viewpoint of how



**FIGURE 7.** Idealized perturbations on reaction barriers resulting in high selectivity, and a more common case where selectivity is not improved (please see text).



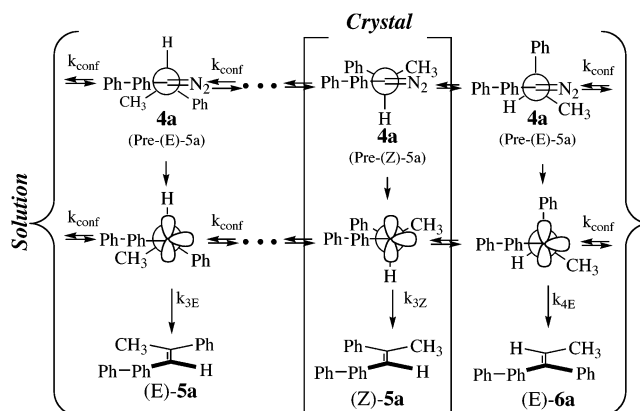
**FIGURE 8.** Disclosure of a reaction coordinate illustrating a correlation between reactant and transition states.

crystals determine the feasibility and selectivity of chemical reactions.

The mathematical theory of communication describes the information contained in a given source.<sup>48</sup> Examples of information sources are the English language, the Morse and binary codes, *Accounts of Chemical Research*, and the Library of Congress. Communication theory was also formulated to describe the constitution of messages and their transmission through communication channels, such as telegraph or phone lines. A schematic illustration of the use of statistical entropy in reacting systems is shown in Figure 8. It is explicitly recognized that a reactant *R* may exist in a wide variety of states  $P_1, P_2, \dots, P_i$ , representing conformations, spin states, molecular vibrations, lattice phonons, and all other states describing the system. The mathematical relationship between statistical entropy  $S$  and the population fraction  $X_i$  of the states  $P_i$  is given by  $S = -\sum X_i \log X_i$ . The magnitude of  $S$  depends on the number of states and on their relative populations. Large values describe systems with a large number of evenly occupied states, which are said to have “high information content” or “large amount of choice”. Small values indicate that only a few states are occupied. Statistical entropy is directly related to homogeneity. While a nearly perfect crystal near zero Kelvin has low statistical entropy with molecules restricted within a limited number of states, liquids and amorphous solids have molecules in a large number of states and have high statistical entropy.

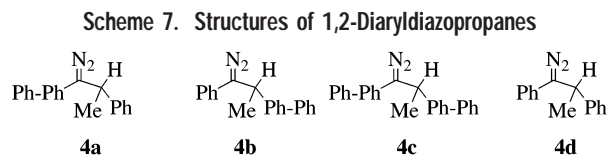
Although the statistical entropy of chemically reacting systems is very complex and difficult to sort and to describe, information theory suggests that not all the

**Scheme 6.** Reactions in Crystals Occur with Lower Statistical Entropy than Reactions in Solution



information in a system must be part of a message. The ink, font, line spacing, and page numbers in this paper are part of the information contained in this article but not part of its message. The link between statistical entropy and information theory can be further illustrated with Figure 8 by considering an analogy between a chemical reaction and a message. First we disclose the reaction coordinate along the reactant surface to illustrate that reactions A and B correlate with the reactant states  $P_1$  and  $P_4$ . This correlation must be based on prior mechanistic knowledge. While the population of  $P_1$  and  $P_4$  in fluids is given by their respective Boltzman factors, crystallization reduces the statistical entropy of the system by freezing equilibration. If *R* crystallizes in state  $P_2$ , no reaction can be observed, and the crystal can be said to have information of no chemical reaction, or no “reactivity messages”. On the other hand, crystallization of *R* in state  $P_4$  would allow reaction B to proceed with perfect selectivity. Reaction A would require a polymorph crystal that selects the reactant in the state  $P_1$ . We conclude that all crystals reduce the amount of choice available in solution, but that only a few have information leading to chemical reactions, or “reactivity messages”.

**B. Information Content in Crystalline 1,2-Diphenyldiazoalkanes.** The statistical entropy in crystals of diazo **4a** is extremely limited when compared to that present in solution (Scheme 6). Bimolecular reactions are prevented by unfavorable alignment between prospective reaction centers and by exclusion of additional reagents from the crystal lattice. While all conformational states are represented in solution (high statistical entropy) and all possible products can form, only one conformation and one product can be present in the crystal (low statistical entropy). High statistical entropy implies information content for many chemical reactions, and many “chemical messages”. Crystals of **4a** select a particular conformation, and their rigidity maintains the structural information from reactant to product. The conformation present in crystals of **4a** aligns the migrating hydrogen parallel to the empty p-orbital and keeps the two aryl groups gauche to each other when the singlet carbene is formed (conformer



Pre-(*Z*)-5a, Scheme 6). The formation **5aZ** is a result of the information contained and maintained in crystals of **4a**.

## From Molecular Structures to Reactive Crystals

On the basis of the discussion and analysis presented in the previous sections, one may gain an intuitive view of how crystals prevent or facilitate certain chemical reactions based on their information content. Interestingly, the information present in a crystal is itself determined by the molecular structure of the reactant and the conditions used for crystal growth. For that reason, reactions in crystals may be engineered with information that is largely contained at the molecular level. We expect greatest success with unimolecular rearrangements from crystalline substrates that form species with high energy content, such as carbenes and biradicals. Given that (1) most neutral molecules crystallize in their lowest energy conformations<sup>49</sup> and that (2) lowest energy conformers can be predicted with reasonable accuracy by modern computational methods, we believe that reactions known to occur with high stereoelectronic control should be identifiable with reasonable success.

As a modest test of this hypothesis, we investigated a set of diazo compounds related to **4a** (Scheme 7). We established their lowest-energy conformations by molecular mechanics calculations, and in two cases we confirmed those conformations by single-crystal X-ray diffraction. On the basis of the reaction mechanism for 1,2-*R* migrations and assuming reactions from gas-phase lowest energy conformers, we predicted 1,2-*H* shifts to give the (*Z*)-alkenes in all cases.

The results were extremely satisfying. Solution photochemistry was complex and strongly dependent on solvent, temperature, the presence of oxygen, etc. Structural predictions by molecular mechanics were in close agreement with the X-ray structures in the cases of **4a** and **4b** (Figure 9). But most importantly, the use of information obtained from molecular mechanics and the accepted reaction mechanisms led to the correct prediction in all cases. Furthermore, nearly perfect reaction selectivity (up to >99%) with preference for the predicted (*Z*)-isomer was observed when crystals of **4b–4d** were irradiated with  $\lambda > 380$  nm. The lowest selectivity was observed in crystals of **4d**, which had been previously shown to crystallize with conformational disorder.<sup>50</sup> The importance of crystal homogeneity, as opposed to only rigidity, was confirmed when reactions in amorphous solids yielded complex mixtures.

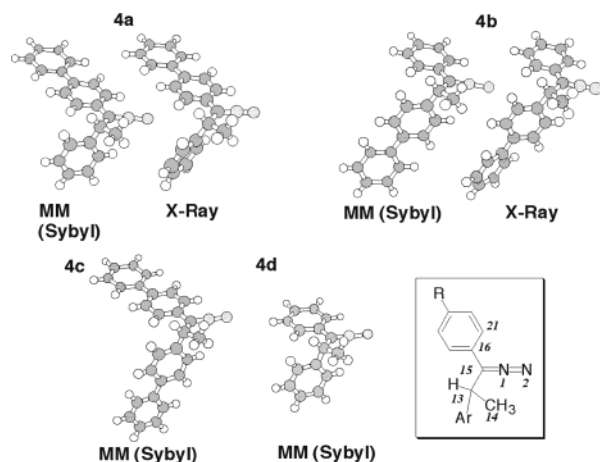


FIGURE 9. (Top) Comparison of molecular mechanics and X-ray structures of compounds **4a** and **4b**. (Bottom) Molecular mechanics structures of **4c** and **4d**.

## Concluding Remarks

In contrast to reactions in solution and gas phase, reactions in crystals proceed under severe structural constraints. Using carbene rearrangements as a test, we have described a relatively simple approach that may help engineer reactions in crystals in a reliable manner. Although we believe that this approach will be transferable to other reaction types, additional research must be done to document the potential and limitations of reactions in crystals. We envision applications of the solid state in solvent-free synthesis and in the development of functional materials.

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