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## Development of Experimental and Theoretical Crystal Lattice Organic Photochemistry: The Quantitative Cavity. Mechanistic and Exploratory Organic Photochemistry<sup>1</sup>

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### ABSTRACT

The photochemistry of organic reactants in the crystalline state has a long history. What has been lacking is comprehensive theory defining what controls the course of these reactions which quite often afford products not obtainable in solution. Also lacking has been solid-state rearrangement chemistry with accompanying theory. In our research over the past two decades we have developed theoretical treatments of solid-state reactivity. This report describes the development of this research from its primitive beginnings to the present.

### Introduction

Our research in crystal lattice organic photochemistry began in 1985. The first publication attempted to treat excited-state reactions quantitatively; however, the approach was primitive in treating excited states with molecular mechanics. Since that time we gradually de-

veloped more sophisticated theoretical approaches. In the course of these studies, a number of experimental findings also resulted. The present writing reviews the development of our research in this endeavor and covers literature efforts only insofar as they are directly relevant to these studies.

### Background

In 1985, solid-state organic chemistry had a large number of examples where the reaction in the crystal was different from that in solution.<sup>2</sup> However, the corresponding theory was mainly qualitative. The reactions investigated generally involved minimal molecular reorganization. Where quantitative, the theoretical treatments focused on the reactant geometry and properties. Nevertheless, the ideas were both stimulating and challenging. Thus, Cohen and Schmidt had proposed that solid-state reactions take place in a cavity composed of surrounding crystal lattice molecules.<sup>3,4</sup> A second concept was that solid-state reactions take place with the least motion,<sup>4</sup> and this has been termed the "topochemical principle". One more quantitative postulate was that, for [2+2] cycloadditions, a distance of 4.2 Å or less between  $\pi$  bonds was required.<sup>2</sup> Still more quantitative treatments of these bimolecular, [2+2] cycloadditions in studies by Thomas and Ramamurthy involved packing potentials in which an empirical van der Waals function is used to assess the energy of the molecular pair in the cavity.<sup>5a,b</sup> Also, Warshel employed an early QM/MM method to assess the properties of an excimer.<sup>5c</sup> These studies focused on some characteristic of one species rather than on the reaction itself. A different approach, often utilized, involved inspection of the proximity of an individual functionality with its nearest neighbor, where that functionality is most important to

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the reaction, as in elegant studies by Lahav and Scheffer.<sup>6</sup> Still another approach involved calculation of cavity volumes in one pioneering study by Gavezzotti.<sup>7</sup> Finally, in fascinating studies on radical-pair reactions, McBride has considered the role of local stress.<sup>8</sup> However, in essentially all of these studies, the methods relied on characteristics of the reactant crystal in order to understand its reactivity. Our aim was to find ways to compare the reacting species in the lattice with the original reactant. This is analogous to ground-state solution chemistry, where it is helpful to compare a transition state with reactant rather than inspecting the proclivities of the reactant alone.

## Discussion

**The Mini-Crystal Lattice and Insertion of the Reacting Species.** In our early research<sup>9</sup> on crystal lattice photochemistry, we had reactant X-ray structures at our disposal, and we thus had the Cartesian coordinates of all atoms of the reactant crystal. Our idea was to take a manageable portion of the crystal lattice, which we termed a “mini-crystal lattice”, and define a central molecule as the reactant. The reactant molecule was to be replaced computationally by a transition structure or an early intermediate along the reaction coordinate. The replacement was effected with optimal overlap with the original structure. The assumption was that the intermediates in these reactions approximate the transition structures. It was postulated that those species which fit best into the mini-crystal lattice are the ones most likely to lead onward to product. In contrast to much of the early crystal lattice chemistry, our reactions were molecular rearrangements which involve massive geometric changes in proceeding from reactant to alternative transition structures.

While the reactant coordinates were available from X-ray data, there was need for the structures, with coordinates, of the reaction intermediates. In this early research, molecular mechanics was often utilized for generating and optimizing the geometry of the reacting species, while both semiempirical and *ab initio* quantum mechanics was used only in a few instances. Clearly, excited-state structures generated with molecular mechanics lack features derived from the molecular electronics. Nevertheless, the predictions proved remarkably correct. At the time, our best measure of fit of the reacting species was overlap with the surrounding neighboring molecules. In addition, the least motion and volume change of the molecule in proceeding from reactant to the first intermediate were determined.

A typical study in this early work contrasted the solution- and solid-state photochemical reactions of five reactants.<sup>9</sup> One example is given in Scheme 1, where in solution pentenol **1** underwent a long-range phenyl migration to afford ketone **6** but in the crystal lattice cyclized to tetrahydropyran and tetrahydrofuran derivatives (**4** and **5**, respectively). The three reactivity indices are for transformation from reactant to the first intermediate, leading to each photoproduct. It was found (see

Scheme 1. Solid-State Modification of the Solution Long-Range Aryl Migration Reaction

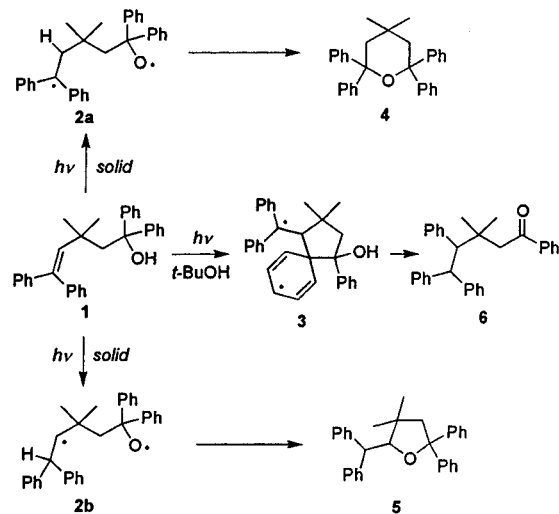


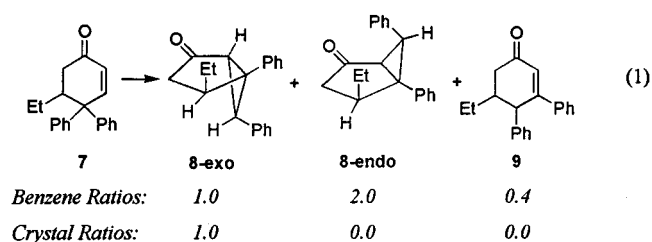
Table 1. Reactivity Indices for Formation of First Intermediates<sup>a</sup> (2a, 2b, 3) from Pentenol 1

photoproduct	RMS motion, Å <sup>b</sup>	Δ-volume, %	Δ-overlap, % <sup>c</sup>
pentanone <b>6</b>	1.00	18	5
tetrahydropyran <b>4</b>	0.20	8	2
tetrahydrofuran <b>5</b>	0.20	8	1

<sup>a</sup> The first intermediates were maximally superimposed on reactants. <sup>b</sup> Sum of non-hydrogen root-mean-square (RMS) atomic displacements. <sup>c</sup> Relative decrease in lattice volume due to van der Waals overlap.

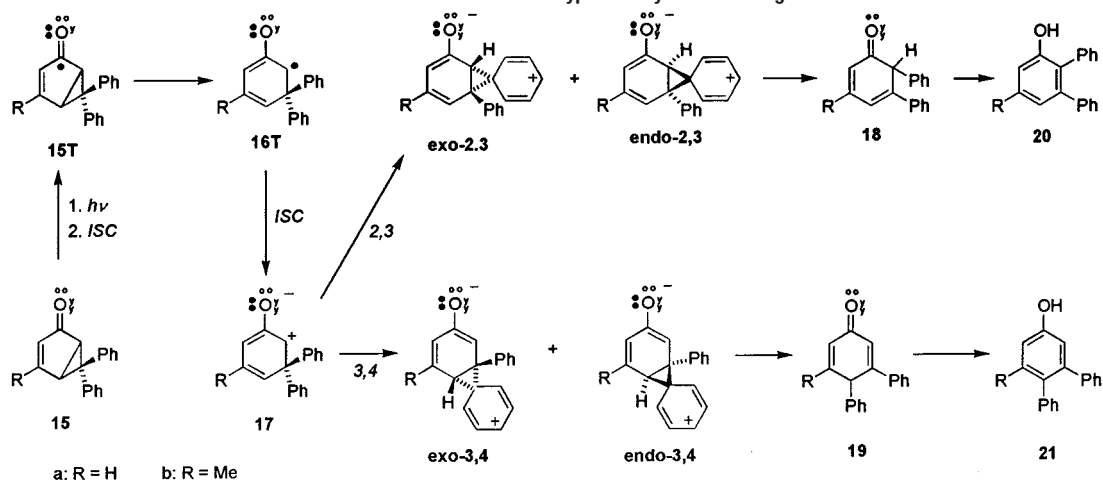
Table 1) that the formation of the solution ketone **6** requires considerably more motion, more of an increase in molecular volume, and more overlap with the neighboring crystal lattice.

**Energetics in Proceeding toward Product: Type B Enone Rearrangements.** A comparison of the different criteria of crystal lattice reactivity was provided in a study of a series of 2- and 5-substituted cyclohexenones.<sup>10,11</sup> These underwent the type B enone rearrangement,<sup>12</sup> which we have studied extensively over the decades. Typical solution versus crystal reaction differences are outlined in eq 1.

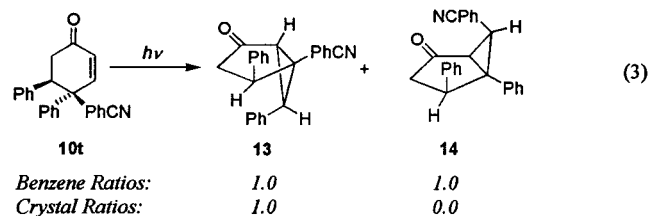
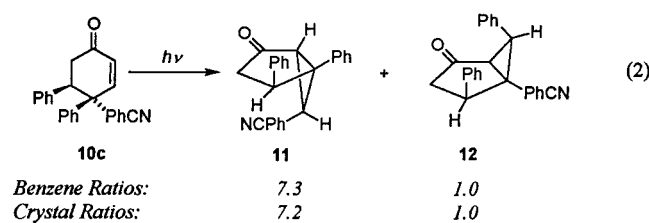


Equations 2 and 3 contrast the solution and crystal lattice reactions for two further examples described in that study. Actually, the study investigated 12 different reactants and thus provided a complete pattern of reactivity to test theory. With one exception, that of **10c**, the product distributions in the crystal lattice chemistry differed from those in solution photochemistry. Clearly, from the synthetic viewpoint, one can obtain, by using solid-state

Scheme 2. Mechanism of the Type B Bicyclic Rearrangement



irradiation, photoproducts which are unobtainable as appreciable products in solution.



Three computational tests were tried. These used that species having the  $\gamma$ -migrating aryl group bridged to the  $\beta$ -carbon as the controlling intermediate (vide infra). The first test was determination of the RMS motion of the reactant atoms in proceeding to this controlling intermediate. The second was determination of the van der Waals overlap of this intermediate with the surrounding lattice. The last was determination of the energy of the “mini-crystal lattice”, in which the central molecule had been replaced optimally by this reacting intermediate. Interestingly, in this study all three criteria successfully correlated with experiment. That least motion was successful is a bit surprising since this approach neglects interaction of the reacting molecule with the crystal environment.

In considering the energetics of these transformations, the reacting species structure was obtained from quantum and molecular mechanics. Optimization of the resulting mini-crystal lattice, however, then was by molecular mechanics. It proved possible to dissect the energy into two components: deformation energy of the reacting species and reacting molecule–lattice interaction energy. Of the two, control of the reaction course was primarily due to deformation of the reacting species.

**The Type B Bicyclic Rearrangement.** Another unique reaction is the type B bicyclic rearrangement.<sup>13</sup> A series of bicyclo[3.1.0]hexen-2-ones were investigated in solution and in the solid state.<sup>14</sup> The basic mechanism is outlined in Scheme 2. This is a rearrangement in which the internal three-ring bond is opened to afford a triplet diradical **16T**, which intersystem crosses to a six-membered ring zwitterion **17** (see Scheme 2), and this then undergoes an aryl 1,2-shift. The electronic configurations are depicted using the notation we introduced in the early 1960s to permit mechanistic description of excited-state reactivity.<sup>15</sup> In solution, endo and exo phenyl groups have equal probability of rearranging due to the planarity of the zwitterion. In contrast, in the crystalline state this no longer is true as a result of the asymmetry of the lattice environment. Additionally, the rearranging phenyl groups have the a priori opportunity of migrating to both C-2 and C-4. The two aryl groups in Scheme 2 are labeled as “endo” or “exo”, depending on their configuration in the original bicyclic reactant. One dramatic solution example is included in Scheme 3, where both the exo and endo *p*-bromophenyl bicyclics lead to the same product distribution by virtue of the common zwitterionic intermediate. In contrast, in the solid state the endo and exo reactants lead to different distributions. Thus, **22-exo** reacted with phenyl migration, while **22-endo** underwent only bromophenyl migration. Throughout, the crystal lattice chemistry leads to a preference for migration of the endo group.<sup>14</sup> This preference, as well as the preferences for a large series of rearrangements of this type, was in accord with minimum  $\Delta$ -overlap and also with minimum  $\Delta$ -energy as determined by molecular mechanics. In contrast, least motion correlated very poorly with experiment for the reactions in this study. (See Table 2.)

**The Inert Gas Shell Model.** The agreement of a fairly large number of crystal lattice transformations with molecular mechanics computations was a bit disconcerting. Such computations assume that the contribution of delocalization effects is minimal. Also, molecular mechanical methods do not permit assignment of multiplicities to the reacting species in the mini-crystal lattice. Thus, a

Scheme 3. Contrast between Solution and Crystal Bicyclic Type B Reactivity

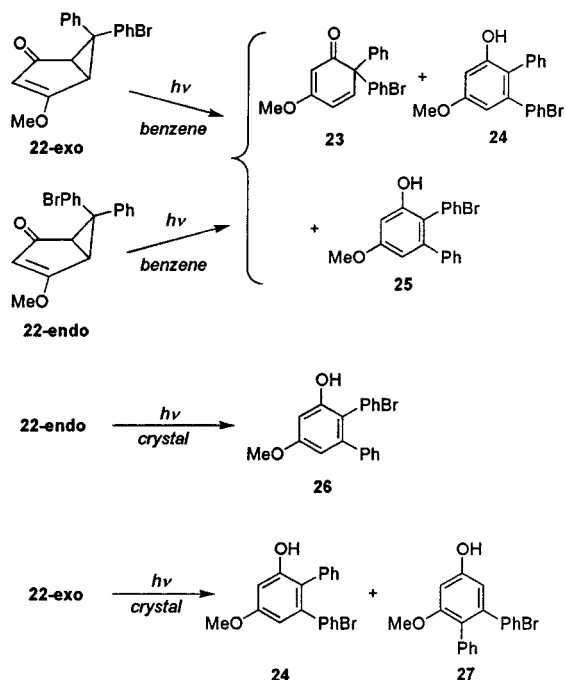


Table 2. Theoretical Treatment of Solid-State Photoreactions of 22-endo and 22-exo

reactant	migrating group	migration energy		overlap		RMS motion	
		C-2	C-4	C-2	C-4	C-2	C-4
<b>22-endo</b>	<i>endo</i> -Br-phenyl	-30.7 <sup>a</sup>	-8.3	17.3	31.3	1.78	1.43
	<i>exo</i> -phenyl	0.8	-14.3	42.9	37.3	1.82	2.15
<b>22-exo</b>	<i>exo</i> -Br-phenyl	-12.7	-12.4	31.9	36.0	1.75	2.17
	<i>endo</i> -phenyl	-26.7	-26.3	16.7	22.9	1.78	1.28

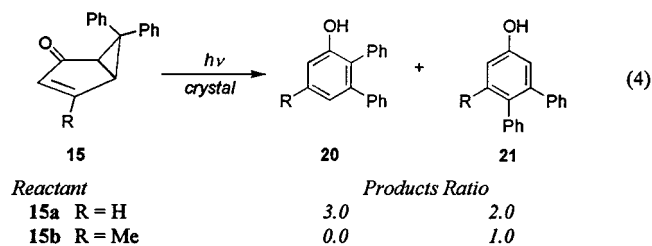
<sup>a</sup> Italics signifies the experimentally observed pathways.

new approach was desired. Clearly, an ab initio computation of mini-crystal lattices composed of a reacting species surrounded by neighboring molecules was impractical because of size. Even a semiempirical computation (e.g., AM1) was not accessible. Thus, the concept of a rigid inert gas shell was developed.

This approach began with determination of the distance between all pairs of atoms, one from the reacting species and one from the neighboring molecules. This utilized programming termed "Pairs".<sup>16</sup> Except for those atoms nearest the central, reacting molecule, all other atoms were then annihilated. Since the remaining atoms then had "dangling" free valences, the hydrogens were computationally converted to helium atoms, and the carbons, oxygens, and nitrogens were converted to neons. The differences in van der Waals radii are small, and in any case, we found that one can just expand the inert gas shell by these differences to take these factors into account. Using Gaussian, it was possible to do ab initio computations on the entirety, reacting species and rigid inert gas shell. Here we are dealing with a rigid, irregularly shaped cavity which, while shaped like the original lattice cavity, nevertheless is an artificial one.

The method was tried on three solid-state reactions, two type B bicyclic rearrangements and one type B enone

rearrangement. The two bicyclic reactants studied were the parent 6,6-diphenylbicyclo[3.1.0]hexenone **15a** and its 3-methyl derivative **15b**. (See eq 4 and Scheme 2.)



The computational results in Table 3 (also see eq 4) show that interesting preference for migration of the endo aryl groups noted earlier for the *p*-bromophenyl cases. However, without isotopic labeling, this cannot be confirmed by experiment, in contrast to the *p*-bromophenyl examples. Equally interesting are the directions of migration of **15a** and **15b**. In the case of parent bicyclic reactant **15a**, a close to equal migration to C-2 and C-4 is predicted and observed experimentally. However, for **15b**, migration to C-4 is a lower energy process than migration to C-2, both experimentally and computationally, a result which contrasts with the solution reaction course.<sup>13</sup>

The type B enone rearrangement studied was the case of 5-ethylcyclohexenone **7** discussed earlier (see eq 1). In this rearrangement, the experimentally observed preferential formation of **8-exo** (see eq 1) is also predicted computationally (see Table 4).

**ONIOM QM/MM Methodology and Host-Guest Reactivity.** It is remarkable how well the irregularly shaped inert gas shell approach (see ref 16) properly predicts crystal lattice photochemistry. Nevertheless, it was suggested by one reviewer of that publication<sup>16</sup> that the inert gas model neglects long-range compression effects; it certainly is artificial. With the idea of getting theory including the crystal lattice neighbors, we proceeded<sup>17</sup> to make use of Morokuma's ONIOM<sup>18</sup> as embedded in Gaussian 98.<sup>19</sup> The method permits dissection of a very large system into three portions, or shells. We desired one to be subject to ab initio quantum mechanical computation and the other two to be subject to molecular mechanics. Our mini-crystal lattice computation is simplified by not needing to sever bonds. Thus, the reacting species was taken as the central shell and subjected to quantum mechanical computation. A set of closely neighboring reactant molecules surrounding the reacting species was taken as the second (i.e., the middle) shell. Finally, an outer shell was comprised of all more distant reactant molecules. This is shown schematically in Figure 1.

The reacting species is subjected to geometric movement and optimization. The second, middle shell of nearest molecules is permitted to move modestly flexibly as well. However, the outer shell is kept rigid. This approach<sup>17</sup> has a number of advantages. First, it permits proper QM computation of excited inner-shell reacting species; molecular mechanics, as used earlier, does not take into account delocalization effects. It really had not been quite realistic, in principle, to assess the energetics of open-shell species such as a triplet using molecular

**Table 3. Energies<sup>a</sup> of Four Alternative Half-Migrated Species from (a) Bicyclic 15a and (b) Bicyclic 15b<sup>b</sup>**

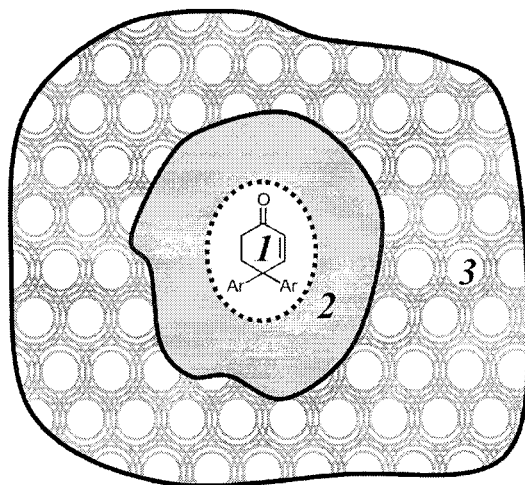
component	endo-2,3	exo-2,3	endo-3,4	exo-3,4
(a) Bicyclic 15a				
compound with shell	-816.28448	-816.78088	-816.87729	-816.81137
shell	-55.92535	-56.42625	-56.51490	-56.45517
compound	-760.35913	-760.35463	-760.36239	-760.35621
<b>experiment:</b>	preferred 60		preferred 40	
(b) Bicyclic 15b				
compound with shell	-855.26722	-855.45976	-855.69397	-855.65673
shell	-56.08549	-56.28772	-56.32353	-56.48572
compound	-799.18173	-799.17204	-799.37044	-799.17101
<b>experiment:</b>			only product	

<sup>a</sup> Energies in hartrees. <sup>b</sup> ROHF/3-21G computations.

**Table 4. Energies<sup>a</sup> of the Two Alternative Half-Migrated Species from Enone 7<sup>b</sup>**

components	cis-endo <sup>c</sup>	trans-exo <sup>d</sup>
compound with shell	-894.56091	-894.71928
shell	-55.55763	-55.68417
compound	-839.00328	-839.03511
<b>experiment</b>		only product

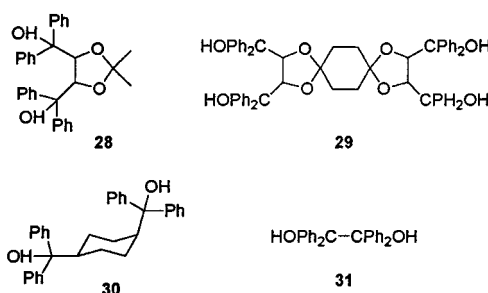
<sup>a</sup> Energies in hartrees. <sup>b</sup> ROHF/3-21G computations. <sup>c</sup> Precursor of **8-endo** in eq 1. <sup>d</sup> Precursor of **8-exo** in eq 1.



**FIGURE 1.** ONIOM treatment of the mini-crystal lattice. 1, Central molecule, ab initio optimized. 2, Nearest neighbors shell, MM optimized with moderated force constants. 3, Outer shell, MM computation but kept frozen.

mechanics. Nevertheless, we can assess the validity of the methods in our very early work which utilized such molecular mechanical methods. Second, the method, in permitting the number of flexible second-shell molecules immediately surrounding the reacting species to be expanded, permits us to assess the importance of crystal lattice relaxation and of long-range stress effects. More recently Garcia-Garibay, Houk, and Scheffer have employed a corresponding molecular mechanics treatment in a very pretty study.<sup>20</sup>

In our publication,<sup>17</sup> we described some new host molecules as well as the crystal lattice photochemistry of molecules entrapped in inclusion compounds. However, the analysis of crystal lattices composed of reactants and host molecules required methodology for generating mini-crystal lattices composed of the host-guest pairs (vide infra). Some of the hosts which have been useful to us are shown in Figure 2. The Seebach-Toda compound **28**



Host	Enantiomer imbedded	Host : guest ratio	Space group
Seebach - Toda <b>28</b>	<i>R</i>	1 : 1	<i>P2<sub>1</sub>2<sub>1</sub>2<sub>1</sub></i>
Seebach - Toda <b>28</b>	<i>S</i>	2 : 1	<i>P2<sub>1</sub>2<sub>1</sub>2<sub>1</sub></i>
Octaphenyltetraol <b>29</b>	<i>S</i>	1 : 1	-
Cyclohexyldiol <b>30</b>	<i>RS</i>	1 : 1	<i>P2<sub>1</sub>/c</i>
Benzopinacol <b>31</b>	<i>RS</i>	1 : 1	<i>Pbca</i>

**FIGURE 2.** Four hosts used for inclusion compound studies.

and host **29** are chiral, while hosts **30** and **31** are not. All of these form inclusion compounds with 4-*p*-cyanophenyl-4-phenylcyclohexenone **32**. The reactions are outlined in Scheme 4. The Seebach-Toda host **28** formed both 1:1 and 2:1 inclusion complexes. The 1:1 inclusion complex led to one enantiomer of the trans-bicyclic **33a** in which a cyanophenyl group had migrated. In contrast, the octaphenyltetraol host **29**, which formed a 1:1 complex, afforded the other enantiomer, **33b**. Especially interesting was the observation that the cyclohexyldiol host **30** gave only phenyl migration product **34**. In this case, the host **30** is achiral, and the product was racemic. (See Scheme 4.)

With these results, using ICPack,<sup>21</sup> we created a mini-lattice from X-ray data in each case and dissected it into the usual three shells. Using ONIOM, we then obtained the optimized energies listed in Table 5. The total ONIOM energy is given in eq 5. However, the current version of

$$E_{\text{tot}}(\text{ONIOM}) = E_{\text{molecule}}(\text{ab initio}) + E_{\text{middle shell}}(\text{MM}) + E_{\text{outer shell}}(\text{MM}) \quad (5)$$

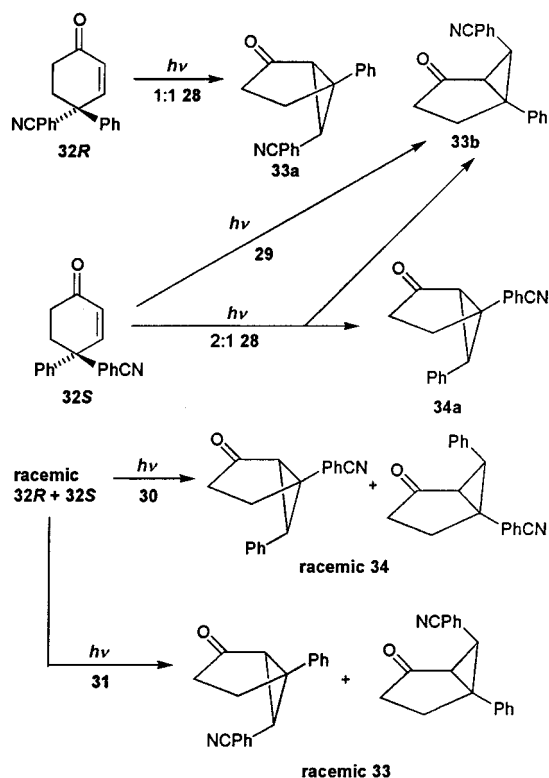
ONIOM utilizes molecular mechanics force fields which are not as well suited for typical organic molecules as is MM3. One can improve the final energy by replacing these force fields with those used in MM3 by means of eq 6. It

$$E_{\text{tot}}(\text{improved}) = E_{\text{molecule}}(\text{ab initio}) + E_{\text{total}}(\text{MM3}) - E_{\text{molecule}}(\text{MM3}) \quad (6)$$

**Table 5. ONIOM Energies of Mini-Crystal Lattices with Alternative Migration Intermediates<sup>a</sup>**

inclusion compound	phenyl migration intermediate <b>36</b> <sup>b</sup>	cyanophenyl migration intermediate <b>35</b> <sup>b</sup>	$\Delta$ -energy <sup>c</sup>	experiment
Seebach–Toda <b>32</b> (1:1)	−855.4092	−855.4249	9.9	CNPh migration
cyclohexyldiol <b>34</b>	−855.5556	−855.5523	−2.1	phenyl migration
benzopinacol <b>35</b>	−855.2728	−855.2893	10.4	CNPh migration

<sup>a</sup> ONIOM(ROHF/6-31G\*:MM3). <sup>b</sup> Energies in hartrees (627.5 kcal/mol). <sup>c</sup> In kilocalories per mole.

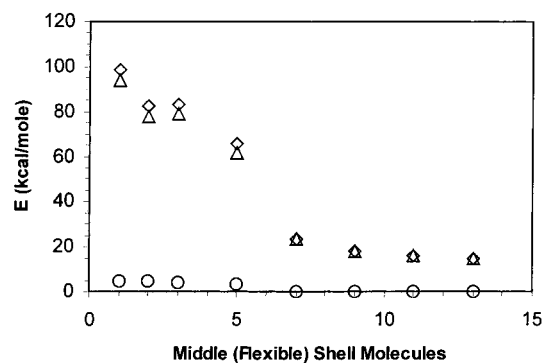
**Scheme 4. Control of Regioselectivity and Chirality by Use of Alternative Hosts**

is with eq 6 that the energies in Table 5 were obtained. In this table, a negative  $\Delta$ -energy corresponds to a preferential phenyl migration, while a positive value signifies prediction of a cyanophenyl shift.

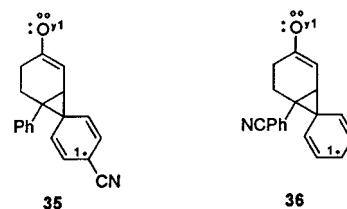
This ONIOM treatment leads to results which are in excellent accord with experimental observation and obviates the philosophical limitations of the inert gas shell approach. The method affords results in instances where simple molecular mechanics fails.

One further interesting result is obtained by extending the interface between the two MM shells in such a way that the reacting species is surrounded by more molecules which are subject to geometry optimization and thus to relaxation. Consideration of the effect on total energy by having more shell molecules able to flexibly optimize revealed that stress by distant molecules falls off quickly with distance. Calculated energies as a function of the number of shell molecules are shown in Figure 3, dealing with a 1:1 complex with the Seebach–Toda compound **28**.

Another result which is of consequence is the finding that least motion fails for the rearrangements of inclusion complexes of enone **32** with the Seebach–Toda host **28** (see Scheme 4). This has been noted to be unsuccessful



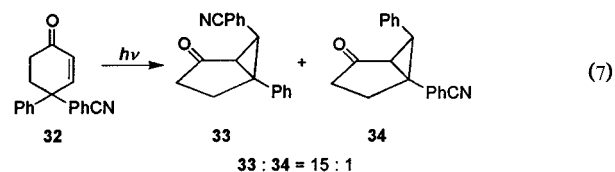
**FIGURE 3.** Energy of the half-migrated triplet diradicals **35** and **36** versus number of flexible second-shell molecules (ab initio values). (◇) Phenyl migration, (○) cyanophenyl migration, and (Δ) the energy difference for the two pathways.



**FIGURE 4.** Alternative triplet diradical intermediates. Solid dots represent  $\pi$ -system electrons,  $y$ 's are  $p_y$ -orbital electrons, and circles are the collinear  $sp$ -hybrid electrons.

in the type B bicyclic rearrangement as well (vide supra).<sup>14</sup> The concept, often termed the “topochemical principle”, seems successful for processes involving relatively little motion, such as  $2\pi+2\pi$  cycloadditions, but not reliable for complex rearrangements.

**Dimorphs and Solid-State Kinetics.** A fascinating result started with the observation that 4-phenyl-4-*p*-cyanophenylcyclohexenone **32** crystallizes in two modifications.<sup>22</sup> Normally in solution the cyanophenyl migration is preferred 15:1, as depicted in eq 7.<sup>12</sup> This results from the



greater delocalization (2.5 kcal/mol<sup>17</sup>) available in the initial triplet bridged diradical **35**, which has the *p*-cyano group on the migrating aryl group, compared with species **36**, which has a migrating phenyl group. (See Figure 4.) The first of the two dimorphs has  $P2_1/c$  symmetry and was termed “crystal A”. On photolysis, this afforded only the *p*-cyanophenyl-migrated bicyclic **33** and lacked the minor phenyl-migrated product **34**. A more exciting result

was encountered for "crystal B" with  $C2/c$  symmetry. This crystalline modification underwent only phenyl migration, a result which demonstrates that the crystal forces involved exceed the 2.5 kcal/mol solution preference by more than a factor of 2. An important observation was that the preference for phenyl migration was observed only during the first 16% conversion ("stage 1"). Beyond this point ("stage 2"), a consistent 1:1 regioselectivity resulted.<sup>22</sup>

However, the QM/MM mini-crystal lattice treatment of crystal B seemed not to predict preferential phenyl migration. The crystal was initially thought to be somewhat disordered. However, a proper analysis of the X-ray data revealed the source of the apparent disorder. Thus, the space group is centrosymmetric with enantiomers arranged in pairs throughout the crystal. However, with the spatial similarity of the ethano and vinyl groups, the observation of some nonmatching enantiomers throughout the crystal was not surprising.

Adjacent to each enone molecule there was encountered one nonmatching enantiomer. The most obvious interpretation was that, with a nonmatching neighbor, the molecule reacted rapidly. However, when all such molecules were exhausted and each molecule also had a product molecule as a neighbor, the rate decreased and a new (1:1) regioselectivity resulted. This interpretation was confirmed by use of the "pairs analysis"<sup>22</sup> (vide supra) of the mini-crystal lattice with an embedded half-migrated species. It was found that the nearest atoms uniquely belonged to the *only* neighbor, which, upon replacement by the "wrong" enantiomer, led to computational prediction of preferential phenyl migration.

To better describe the crystal lattice reactivity, solid-state kinetics of the reaction was developed. Here, eq 8 gives the conversion as a function of composition. This is

$$C = \text{Ph1} + \text{Ph2} + \text{CN2} \quad (8)$$

(three product components giving conversion)

the sum of all product components: the amount of phenyl-migrated product in "stage 1" (i.e., Ph1), the amount of phenyl migration in stage 2 (Ph2), and the amount of cyanophenyl migration in stage 2 (CN2). Equation 9 gives the ratio of total phenyl migration in the two stages divided by the amount of cyanophenyl migration product, which occurs only in stage 2. Then, eq 10 is

$$R = (\text{Ph1} + \text{Ph2})/\text{CN2} \quad (9)$$

(ratio of phenyl to cyanophenyl products)

derived from eqs 8 and 9. A plot of the ratio of the two

$$R = \text{Ph1}(R + 1)/C + (\text{Ph2}/\text{CN2}) \quad (10)$$

regioisomeric products  $R$  versus  $(R + 1)/C$  (i.e., the ratio plus unity divided by the conversion) should be, and is, linear. (See Figure 5.) The slope is Ph1 or the amount of phenyl-migrated isomer in stage 1, and the intercept gives the ratio  $(\text{Ph2}/\text{CN2})$  of phenyl to cyanophenyl migration in stage 2. A slope of 15.6 was obtained, quite in agreement with the observation that the regioselectivity changes at

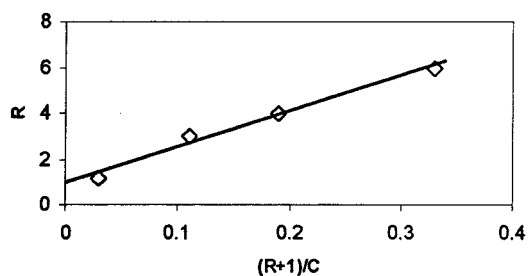
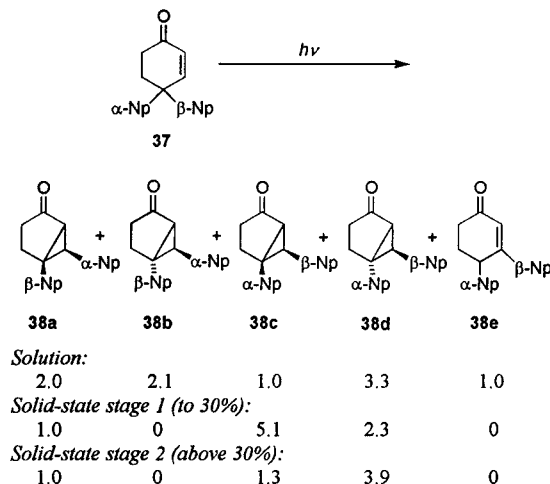


FIGURE 5. Plot of phenyl to cyanophenyl migration ratio  $R$  versus  $(R + 1)/C$ .

Scheme 5. Solution- and Solid-State Product Distributions for 4- $\alpha$ -Naphthyl-4- $\beta$ -naphthylcyclohexenone **37**



16% (i.e., Ph1 equals 16). The intercept of 0.95 obtained is also in agreement with the 1:1 regioselectivity in the second stage of the reaction. Of interest is the knowledge that, with five neighbors close to each reactant molecule, at 16% conversion, 96% (i.e.,  $(5 + 1) \times 16$ ) of the reactant molecules with wrong enantiomer neighbors have reacted.

**The General Concept of Stages.** With the dimorphs **32** example in hand, it seemed that many crystal lattice reactions might proceed in stages. Thus, we began to investigate a number of reactions whose chemistry appeared to vary with extent of conversion.<sup>23</sup> It was concluded that, for a large variety of crystal lattice processes, the reactions do, indeed, proceed in stages, each stage having its own unique reaction course. Scheme 5 provides one example, that of 4- $\alpha$ -naphthyl-4- $\beta$ -naphthylcyclohexenone **37**. We see a dramatic change in reaction selectivity in proceeding from stage 1 to stage 2. Figure 6 gives the plot of product distribution versus conversion. Over each stage there is the remarkable linearity anticipated for a fixed lattice structure. The melting point behavior provided further evidence indicative of phase changes. The reactant's sharp melting point commonly becomes broad or diminished as stage 1 begins, but at the point where stage 1 ends and stage 2 begins, the melting point suddenly becomes sharp, thus characteristic of a new ordering of the crystal lattice.

Our interpretation of the phenomenon here is that those original reactant molecules not adjacent to product molecules react rapidly. Once every reactant molecule

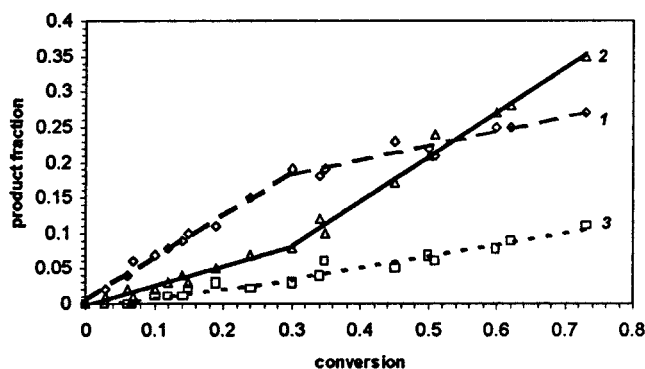


FIGURE 6. Plot of regioselectivity versus extent of conversion for enone **37**. Plot 1 corresponds to product **38c**, plot 2 corresponds to **38d**, and plot 3 corresponds to **38a**.

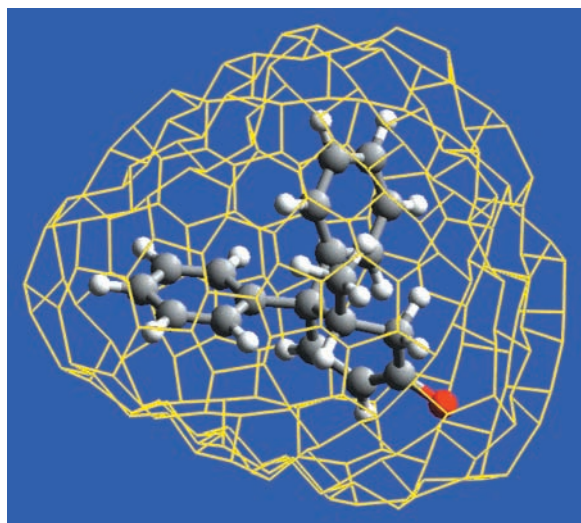


FIGURE 7. Perspective view of a quantitative reaction cavity with a central reacting molecule (5-methyl-4,4-diphenylcyclohexenone).

finds itself adjacent to one product molecule, stage 1 is complete, and the less reactive crystal thus formed begins to react in stage 2. While in some cases there is an immediate change in melting behavior as reactant molecules find their neighbor to have changed, in other cases this melting behavior may be delayed if there is a large ratio of unreacted neighbors to reacted ones. This situation for reactant **37** is different from that of the dimorphs discussed above, where disordered molecules in the reactant crystal played a role. Nevertheless, the philosophy is the same.<sup>24</sup>

We do need to recognize that the phenomenon of stages is characteristic of photochemical reactions involving appreciable changes in molecular size or shape. Thus, for [2+2] cycloadditions, for example, the crystal is more likely to maintain its integrity and maintain a constant reaction course throughout the conversion.

## Conclusion

Treating crystal lattice chemistry on a quantitative basis with an analytical determination of the geometry of the reaction cavity seems necessary for proper understanding of this solid-state chemistry. Figure 7 gives a perspective view of a typical quantitative cavity.<sup>25</sup> There is no inherent

reason solid-state kinetics should not be as accessible as in the case of solution reactions. The intriguing aspect of our finding of stage crystal chemistry is the prospect that there will be cases where only in a second, or later, stage may one find a product whose synthesis is desired. Overall, the exciting future promised by solid-state photochemistry is the ability to obtain products not available from solution chemistry, controlled by cavity effects rather than just by unimolecular electronic factors.

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- (25) The compound selected for presentation is 5-methyl-4,4-diphenylcyclohexenone (ref 11).

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