General Predictor for Photoreactivity in Crystal Lattices: Molecular Mechanics in Crystalline Media and Lock and Key Control. Reaction Examples[1]

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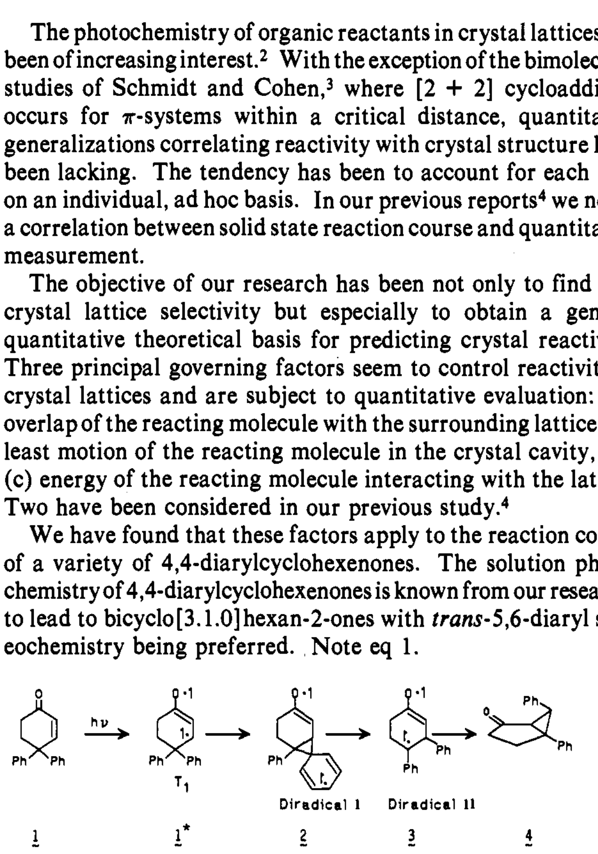
The photochemistry of organic reactants in crystal lattices has been of increasing interest.[2] With the exception of the bimolecular studies of Schmidt and Cohen,[3] where [2 + 2] cycloaddition occurs for π-systems within a critical distance, quantitative generalizations correlating reactivity with crystal structure have been lacking. The tendency has been to account for each case on an individual, ad hoc basis. In our previous reports[4] we noted a correlation between solid state reaction course and quantitative measurement.

The objective of our research has been not only to find new crystal lattice selectivity but especially to obtain a general quantitative theoretical basis for predicting crystal reactivity. Three principal governing factors seem to control reactivity in crystal lattices and are subject to quantitative evaluation: (a) overlap of the reacting molecule with the surrounding lattice, (b) least motion of the reacting molecule in the crystal cavity, and (c) energy of the reacting molecule interacting with the lattice. Two have been considered in our previous study.[4]

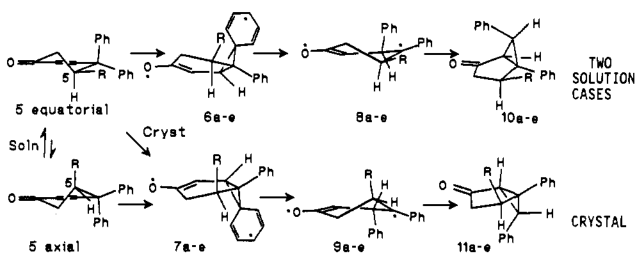
We have found that these factors apply to the reaction course of a variety of 4,4-diarylcyclohexenones. The solution photochemistry of 4,4-diarylcyclohexenones is known from our research[5] to lead to bicyclo[3.1.0]hexan-2-ones with *trans*-5,6-diaryl stereochemistry being preferred. Note eq 1.



(1)

We selected five such cyclohexenones substituted at C-5 and with differing crystal lattices and space groups with the idea of determining which phenyl group migrates in each crystal lattice. In solution this is controlled by ordinary unimolecular energetics while, in crystalline media, crystal lattice forces often dominate and inhibit what would otherwise be a low-energy, facile mechanism. For all five enone reactants[6]—with the C-5 substituent being methyl, ethyl, isopropyl, phenyl, and *tert*-butyl (**5a–e**)—MM3 molecular mechanics computation and NMR analysis indicated a preference in solution for the 5-R equatorial half-chair conformation despite a disinclination for the gauche arrangement of the C-5 substituents which bisect the Ph–C–Ph angle in this conformation (note Scheme 1). The calculated (MM3) equatorial preferences were 0.35 kcal/mol for *tert*-butyl, 0.74 for phenyl, 1.94 for isopropyl, 1.59 for ethyl, and 1.16 for methyl, and the NMR coupling constants supported this view. Counterpart X-ray analyses[6] of the crystalline enone reactants showed half-chairs with equatorial C-5 substituents.

Scheme 1. Stereochemistry of the Phenylenone Rearrangement[a]



[a] **a**, R = Me; **b**, R = Et; **c**, R = *i*-Pr; **d**, R = Ph; **e**, R = *tert*-Bu.

Table 1. Exo:Endo Product Ratios in Solution and in the Crystalline State

	5a (Me)[a]	**5b** (Et)	**5c** (*i*-Pr)	**5d** (Ph)	**5e** (*t*-Bu)
soln[b]	1:2.5	1:2.0	1.4:1	1.2:1	10:1
crystal	6.3:1	exo only	exo only	exo only	exo only

[a] R is in parentheses. [b] Some minor amounts of 3,4-diphenylcyclohexenones were also isolated.

Irradiation of the five enones (**5a–e**) in benzene led to the corresponding bicyclo[3.1.0] ketone stereoisomers. For the C-5 methyl and ethyl substituents (i.e., **5a** and **5b**), there was a preference for the endo-R photoproducts (**10a** and **10b**). However, for isopropyl, phenyl, and *tert*-butyl reactants (i.e., **5c**, **5d**, and **5e**), exo-R products **11c**, **11d**, and **11e** were formed in excess; note Table 1. From this we can conclude, as seen in Scheme 1, that, for methyl and ethyl (**5a** and **5b**) substitution, the phenyl cis to the C-5 substituent migrates while, for the remaining groups (**5c–e**), the trans phenyl migrates in preference.

In contrast, the photolyses in the crystal lattices of enones **5b–e** revealed a single stereochemistry of the equatorial phenyl initially trans to the alkyl group (cf. Scheme 1). Table 1 lists these dramatic differences between the solution and the crystal-lattice stereochemistry.

In doing crystal molecular mechanics we first obtained the space group symmetry and atomic coordinates from X-ray studies. (i) A "mini crystal lattice" composed of 18 or more molecules was generated computationally with the central molecule totally surrounded by all those complete neighboring molecules within 5 Å.[7] (ii) This was followed by extraction of the central molecule and (iii) insertion of the various reacting species of interest. For the reacting molecule we focused attention on "diradical I" (**2**) in eq 1 (also **6** and **7** in Scheme 1). The geometries of these reacting intermediates were obtained using molecular mechanics and AM1.[8] Each generated reaction intermediate was put into the lattice void with atoms positioned as closely as possible to the corresponding atoms of the extracted reactant without change in

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[1] Part 235 of our general and 171 of our photochemical series. Part 234: Zimmerman, H. E.; O'Brien, M. E. *J. Org. Chem.* **1994**, *59*, 1809–1816.

[2] (a) Weiss, R. G.; Ramamurthy, V.; Hammond, G. *Acc. Chem. Res.* **1993**, *26*, 530–536. (b) Ramamurthy, V., Ed. *Photochemistry in Organized and Constrained Media*; VCH: New York, 1991.

[3] (a) Schmidt, G. M. J. *Solid State Photochemistry*; Ginsberg, D., Ed.; Verlag Chemie: New York, 1976. (b) Cohen, M. D.; Schmidt, G. M. J. *J. Chem. Soc.* **1964**, 1996–2000.

[4] (a) For unimolecular reactions especially, previous investigations have generally used qualitative discussion. (b) Zimmerman, H. E.; Zuraw, M. J. *J. Am. Chem. Soc.* **1989**, *111*, 2358–2361. (c) Zimmerman, H. E.; Zuraw, M. J. *J. Am. Chem. Soc.* **1989**, *111*, 7974–7989.

[5] (a) Zimmerman, H. E.; Wilson, J. W. *J. Am. Chem. Soc.* **1964**, *86*, 4036–4042. (b) Zimmerman, H. E.; Hancock, K. G. *J. Am. Chem. Soc.* **1968**, *90*, 3749–3760. (c) Zimmerman, H. E.; Rieke, R. D.; Scheffer, J. R. *J. Am. Chem. Soc.* **1967**, *89*, 2033–2047. (d) Zimmerman, H. E.; Sam, D. J. *J. Am. Chem. Soc.* **1966**, *88*, 4114–4116. (e) Zimmerman, H. E.; Sam, D. J. *J. Am. Chem. Soc.* **1966**, *88*, 4905–4914. (f) Zimmerman, H. E.; Morse, R. L. *J. Am. Chem. Soc.* **1968**, *90*, 954–966. (g) Zimmerman, H. E.; King, R. K.; Xu, J.-H.; Caufield, C. E. *J. Am. Chem. Soc.* **1985**, *107*, 7724–7732. (h) Zimmerman, H. E.; Solomon, R. D. *J. Am. Chem. Soc.* **1986**, *108*, 6276–6289.

[6] Synthetic details will be reported in our full paper; all new compounds afforded satisfactory characterization. Product configurations derived from two X-rays and four stereoselective syntheses. X-ray detail is in the supplementary material.

[7] Programming was developed to build up a crystal lattice with whole molecules according to X-ray information.

[8] (a) Allinger, N. L. MM3, University of Georgia, Dec 1990. (b) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902–3909 (MOPAC Vers 6.0). (c) Triplet diradical centers were taken as sp^2 and checked with AM1 by comparison of geometry and energy differences obtained by the two methods.

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Table 2. Axial vs Equatorial Phenyl Migration Consequences of Diradical I Overlaps, Motion, and Energies

R	overlap with lattice (Å^3) axial:equat	rms motion (Å) axial:equat	Δ interaction[9] with lattice (kcal/mol) axial:equat
Me (**5a**)	20.4 : 13.8	1.40 : 0.74	33.9 : 27.1
Et (**5b**)	23.2 : 14.2	1.48 : 0.71	42.4 : 27.0
i-Pr (**5c**)	17.3 : 12.8	1.46 : 0.70	38.4 : 24.1
Ph (**5d**)	29.4 : 19.4	1.81 : 0.84	45.8 : 29.8
t-Bu (**5e**)	16.9 : 7.7	1.05 : 0.46	30.8 : 12.0

molecular geometry. (iv) Then the energy of the inserted species (diradical I) was optimized with MM3,[9] the lattice being kept rigid. These energies, given in Table 2 (column 3), nicely predict the observed reaction stereochemistry.

Least motion[4,10] was also found to operate reliably as a predictor of reactivity. In this, each diradical I was superimposed on the corresponding enone reactant. Then the displacements of each reactant atom required to afford diradical I were determined. The total motion was evaluated in root mean square form. Note Table 2. Again the correlation with observation was good.

Van der Waals overlap of the inserted reacting species, here diradical I, with the surrounding crystal lattice provided (see Table 2) another useful criterion. Minimum overlap, the third criterion, corresponded to the experimentally observed reactions.

While our study tried to avoid ad hoc rationales for the observed crystal regioselectivities, we did note several interesting facets. Surprisingly, it is the initially equatorial phenyl group which migrates to the β-carbon. However, the initially axial phenyl moiety has its π-system oriented sidewise and virtually orthogonally to the β-carbon p orbital while the equatorial phenyl group's π orbitals are aimed properly at the β-carbon. Thus overlap considerations suggest a preference for equatorial migration; however, there are concerns about the amount of motion required. On the other hand, axial phenyl twisting to give the required orbital overlap also requires considerable molecular motion. The weighting of these factors is not obvious from qualitative reasoning. Hence, the need for our quantitative treatment is illustrated.

A simple guide to reactivity is a "lock and key" representation of the lattice and the reacting molecule. In this representation the long axis of the reactant is taken in the x-direction. With cylindrical coordinates, one finds the x-location, the rotational angle, and the distance from the x-axis (ρ) for the first 10 atoms which project most outward toward the lattice.[11] Then ρ defines the "key". The "lock" values ρ' include the additional distance to the nearest lattice atom. Comparison of the key and lock permits one to ascertain the "fit". One representative example is given in Table 3, and the remaining similar cases are in the supplementary material.

Table 3. Lock (ρ') and Key (ρ) Representation of Three Molecules in the Crystal Lattice of a 5-Phenyl Enone[a]

(a) Enone **5d**

	H39	C35	C42	C33	O1	C5	C3	H6	H43	C31
key:[b] ρ	6.86	5.87	6.20	1.78	8.32	5.45	6.64	4.31	5.80	1.11
lock: ρ'	7.57	6.54	7.03	2.71	9.03	6.18	7.46	5.23	6.54	1.78
fit[c]	0.21	0.20	0.25	0.27	0.21	0.22	0.25	0.27	0.22	0.20

(b) Diradical I of Axial Phenyl Migration **7d**

	H17	C16	H21	C20	C14	H28	C42	C27	C44	H45
key:[b] ρ	4.88	4.96	2.06	3.40	5.53	2.20	7.58	2.31	6.50	5.97
lock: ρ'	4.60	4.72	1.85	3.23	5.33	1.93	7.40	2.10	6.23	5.70
fit:[c]	1.36	1.19	0.99	0.80	0.99	1.32	0.87	1.03	1.31	1.32

(c) Diradical I of Equatorial Phenyl Migration **6d**

	C16	H21	H39	C20	H34	C33	C2	C3	C31	O1
key:[b] ρ	4.81	1.96	6.84	2.87	1.96	2.37	7.33	6.62	1.80	7.89
lock: ρ'	4.81	1.96	6.84	2.87	1.96	2.37	7.33	6.62	1.80	7.89
fit:[c]	0.57	0.90	0.90	0.84	1.19	1.19	0.81	0.66	0.87	0.85

[a] The numbering scheme is as follows: C2, C=O; C3, α-vinyl; C5, β-vinyl; C14, *o-cis*-Ph; C16, *m-cis*-Ph; C20, *m-cis*-Ph; C27, *m-trans*-Ph; C31, *m-trans*-Ph; C33, *o-trans*-Ph; C35, *ipso*-5-Ph; C42, *m*-5-Ph; C44, *o*-5-Ph; H6, β-vinyl; H17, *m-cis*-Ph; H21, *m-cis*-Ph; H28, *m-trans*-Ph; H34, *o-trans*-Ph; H39, *p*-5-Ph; H43, *m*-5-Ph; H45, *o*-5-Ph; O1, C=O. Drawings, numbering, and tables for all diradicals I are in the supplementary material. [b] See footnote 11. [c] Excess over van der Waals overlap.

In summary, it is clear that molecular motion in a crystal lattice is energetically controlled, and that this can be assessed in several ways. However, it is not just a single interaction responsible for controlling reactivity but, rather, the totality of the fit of the reacting molecule. The relationship to the enzyme host–guest problem is clear.

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Supplementary Material Available: "Lock and key" table for all compounds studied, computational data for second molecular structures for three lattices, molecular structures with numbering, and details of X-ray structural determinations (67 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(9) (a) Local minima were avoided by utilization of an initial "flexible superposition"[9b,c] in which all nonring dihedrals of the intermediate are modified to give this species the best rms fit to the extracted molecule followed by MM3 minimization of the single molecule in the crystal lattice. (b) Still, W. C.; Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Lipton, M.; Liskamp, R.; Chang, G.; Hendrickson, T.; DeGunst, F.; Hasel, W. MacroModel V3.5, Department of Chemistry, Columbia University, New York, NY 10027. (c) Zimmerman, H. E.; St. Clair, J. Flexit, Program to do flexible superpositions, determine rms variations, and perform related geometric operations.

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(11) All keys are normalized by the same factor. That key leading to product is taken as the reference. The normalization factor is determined by the reference (i.e., reaction) key and the lock dimensions using $\rho(\text{key},j) = \rho_0(\text{key\_o},j) - [\rho'(\text{lock},j) - \rho(\text{key\_o},j)]\sum_j[\rho'(\text{lock},j) - \rho(\text{key\_ref},j)]/\sum_j[\rho'(\text{lock},j) - \rho(\text{key\_o},j)]$, where j is the value along the x-axis, key_o designates the unnormalized key, key_ref designates the reference key, and lock indicates the lattice, or lock.