

Computational Prediction of the Enantioselectivity of a Solid-State Photoreaction

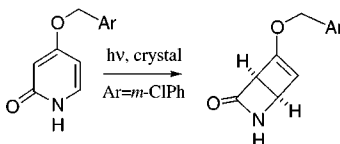
Miguel A. Garcia-Garibay,^{*,†} K. N. Houk,^{*,†,§} Amy E. Keating,[†] Clair J. Cheer,[‡] Mordechai Leibovitch,[‡] John R. Scheffer,^{*,‡,||} and Lian-Chung Wu[‡]

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569, and Department of Chemistry, University of British Columbia, Vancouver, Canada V6T 1Z1

mgg@chem.ucla.edu

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ABSTRACT



To better understand the forces controlling chemical reactions in crystals, the absolute asymmetric photorearrangement of 4-*m*-chlorobenzoyloxy-2-pyridone leading to the corresponding enantiomerically enriched (78% ee) β -lactam was modeled computationally using a flexible minilattice consisting of a central reactant and 20 nearest and 72 next-nearest neighbors. The computational results predicted a preference for formation of the (*R,R*)-enantiomer, and this was verified experimentally by absolute configuration correlation studies.

As has been documented repeatedly in the literature,¹ chemical reactions conducted in the crystalline phase are often more regio-, diastereo-, and enantioselective than their solution-phase counterparts. To account for this increased selectivity, the concept of the “reaction cavity” was introduced by Cohen² and subsequently updated by Weiss et al.³ This model visualizes the reaction of a molecule in a crystal as occurring in a cavity bounded by the van der Waals surface of its nearest neighbors, with any large structural changes being resisted by steep nonbonded potentials imposed by the cavity walls. As a result, solid-state reactions

tend to be restricted to least motion pathways that limit the number of possible products.

The first attempt to treat this situation computationally was made by Warshel and Shakked in 1975, who modeled solid-state excimer formation using an SCF-MO technique to describe the excited-state molecules and an empirical non-bonded exponential potential for intermolecular interactions with the rigid lattice neighbors.⁴ A subsequent approach used by Gavezzotti and co-workers,⁵ as well as by Ariel et al.,⁶ begins with an X-ray crystal structure of the reactant and its nearest neighbors and distorts a central molecule in the cluster along a hypothetical reaction path while monitoring changes in its energy of interaction with the stationary lattice. No optimization is involved. Analogous studies by Kearsley and

[†] UCLA.

[‡] UBC.

[§] houk@chem.ucla.edu.

^{||} scheffer@chem.ubc.ca.

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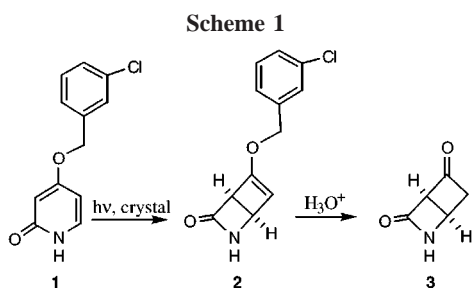
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McBride⁷ and Zimmerman and co-workers⁸ also used an X-ray crystal structure-derived cluster of reactant molecules. The central molecule in the cluster is removed and replaced by a product or intermediate, and the energy of the resulting minilattice is determined using molecular mechanics.

While products and/or intermediates may in some cases mimic transition states, the most accurate results can be expected from modeling the transition state structures themselves inside a minilattice, and this approach was used recently by several of us in a computational analysis of a solid-state carbene rearrangement.⁹ An interesting aspect of this study was the finding that relaxation of the molecules making up the reaction cavity is an integral part of the solid-state process. Since it seems likely that the development of internal stress may be a general feature of crystals undergoing chemical reactions, one of the goals of the work described in this Letter was to compare the performance of models with either flexible or rigid reaction cavities.

The reaction chosen for modeling was the photochemical conversion of 4-*m*-chlorobenzoyloxy-2-pyridone (**1**) into the corresponding β -lactam derivative **2** (Scheme 1).¹⁰ Depend-



ing upon whether the disrotatory electrocyclozation occurs from the top face or the bottom face of the diene system, the process can lead to either of two enantiomeric lactams—the (*R,R*)-enantiomer shown or its mirror image. Conformational effects on the direction of electrocyclozation are minimal in this case, as X-ray crystallography reveals the pyridone ring to be essentially planar. Pyridone **1** belongs to that rare group of compounds that are themselves achiral but which crystallize in chiral space groups, in this case $P2_12_1$.¹¹ Irradiation of a single crystal of pyridone **1** leads to enantiomerically enriched lactam **2** in 78% enantiomeric excess at 2.5% conversion,¹⁰ a so-called “absolute asym-

metric synthesis” in which product chirality is generated from completely achiral reagents.¹²

With the X-ray crystal structure of pyridone **1** in hand,¹⁰ the goal of the modeling study was to predict which of the two possible enantiomeric lactams is the major solid-state photoproduct. The theoretical prediction would then be compared with the experimental result. This required that we establish the absolute configuration of lactam **2**, and this was accomplished by hydrolysis of this material to the corresponding keto-lactam **3**. The (*R,R*)-enantiomer of **3** is known to have a specific rotation of -340.9° ($c = 1.17$, $CHCl_3$), while that of the (*S,S*)-enantiomer is $+338.5^\circ$.¹³ In the event, irradiation of batches of crystals known to be enantiomorphously identical to the crystal whose X-ray structure was determined, followed by acidic hydrolysis in aqueous THF and column chromatography, gave samples of keto-lactam **3** whose optical rotations were unmistakably and reproducibly levorotatory. This establishes that the enantiomorphous form of compound **1** whose crystal structure was determined leads mainly (ca. 89%) to (*R,R*)-**2**.

For the computational approach, the crystal structure of compound **1** was truncated to a minilattice of 20 nearest and 72 next-nearest neighbors surrounding a central (reactant) molecule, X (Figure 1). Because transition states for photo-

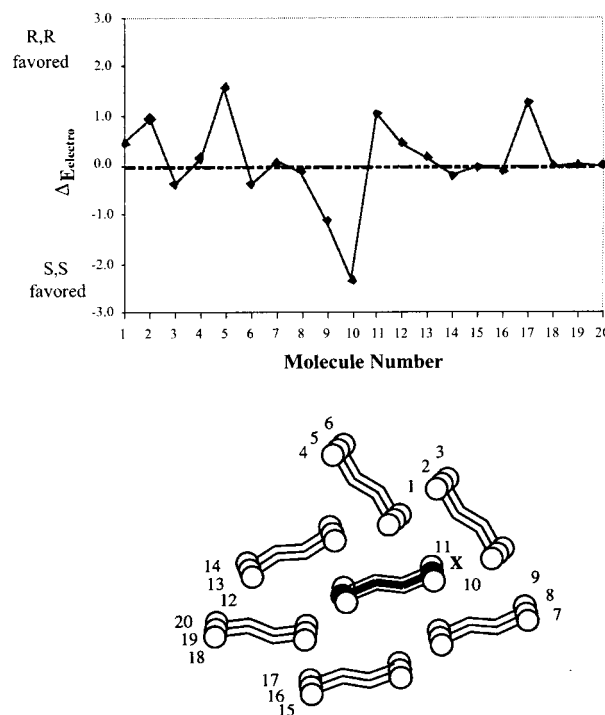


Figure 1. Electrostatic interactions in the solid state.

chemical reactions are difficult to determine by existing ab initio methods, photoproduct **2** was used as a transition state analogue and inserted into the reactant position of the minilattice in both its (*R,R*) and (*S,S*) forms.¹⁴ The energy of the ensemble was then calculated using the MacroModel 5.5 version of AMBER*.¹⁵ Two types of calculations were

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performed. In the first, a rigid lattice of neighbors was maintained, and in the second, the lattice was allowed to relax in the presence of (*R,R*)-**2** and (*S,S*)-**2**.

When the two possible products were optimized in a rigid lattice, there was no significant difference in their total energies. Only when the lattice was allowed to relax was a difference of 0.98 kcal/mol in favor of (*R,R*)-**2** observed. The theoretical prediction, which was carried out in advance of the absolute configuration correlation, thus agrees with the experimental result. Table 1 gives a breakdown of the

Table 1. Origins of the Energy Difference ($E_{S,S} - E_{R,R}$) (kcal/mol)

<i>E</i> quantity	$E_{R,R}$	$E_{S,S}$	$E_{S,S} - E_{R,R}$
E_{total}	-854.40	-853.42	0.98
E_{p}	94.44	94.85	0.41
E_{latt}	-888.48	-889.47	-0.99
E_{electro}	-14.91	-13.45	1.46
E_{vdW}	-45.45	-45.35	0.10

total energy into its component parts. E_{p} is the strain energy of each enantiomeric product in its lattice-optimized conformation, E_{latt} is the lattice distortion energy, E_{electro} is the sum of the electrostatic repulsion and attraction energies involving the product and its lattice neighbors, and E_{vdW} is the sum of the nonbonded repulsion and attraction terms between product and lattice.

The dissection of the computed energies into contributing components reveals that a significant portion of the overall preference for the (*R,R*)-enantiomer is due to the more favorable conformation of this product in the crystal (ΔE_{p}). There is also a component of the energy that disfavors the *R* product, that is, the energy of the lattice distortion, ΔE_{latt} .

(12) The first example of an absolute asymmetric synthesis was provided by Penzien, K.; Schmidt, G. M. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 608. For later examples, see: Casell, L.; Garcia-Garibay, M. A.; Scheffer, J. R.; Trotter, J. J. *Chem. Educ.* **1993**, *70*, 785 and references therein.

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The largest contributing factor to ΔE_{total} , however, comes from $\Delta E_{\text{electro}}$, the electrostatic component. This term is the weighted average of a large number of attractive (mainly H-bonding) and repulsive (primarily oxygen–oxygen and oxygen–chlorine) interactions between the products and their lattice neighbors. These are depicted graphically in Figure 1, which is a plot of $\Delta E_{\text{electro}}$ for each of the 20 lattice neighbors shown.

In conclusion, the present computational study emphasizes the importance of including lattice flexibility in calculations of solid-state reactivity. It is also apparent from the present work that, in the absence of a strong conformational bias, the preference for least motion pathways in crystalline media is likely to be a “many body” problem, that is, reaction selectivity derives from the overall effect of a multitude of small interactions of various types. As a result, attempts to rationalize solid-state reactivity by visual inspection of packing diagrams or by consideration of only one or two prominent lattice interactions is necessarily incomplete. Computational approaches appear promising for the investigation of solid-state reactions, and this area is likely to lead to the development of extremely valuable tools for solid-state chemists in the next few years as faster computers and commercial quantum mechanical/molecular mechanics programs become readily available.

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(14) Photoproduct **2** is a reasonable transition state analogue since it contains geometric changes similar to those that occur in the transition state (particularly ring bending), but to an exaggerated extent. This is desirable for the purposes of our calculations since we are looking for small energy differences at the limit of what is detectable with molecular mechanics.

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