

Five decades of mechanistic and exploratory organic photochemistry*

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Abstract: This exposition summarizes a personal perspective on past and current developments in organic photochemistry. It comprises three portions. The first section describes the beginnings of our photochemical studies and how it was possible to relate photochemical reactivity to excited-state electronic structures. The second selectively relates some of the reactions and concepts developed in the intermediate years. Finally, the third portion describes our recent research.

Keywords: mechanistic; organic; photochemistry; Porter Medal.

INTRODUCTION

It is curious that as a graduate student, a postdoctorate, and then as a beginning assistant professor, I found two areas of chemistry to be particularly uninteresting. These were quantum mechanics and photochemistry. The former seemed to apply to the hydrogen atom, and the latter involved the kinetics of a multiplicity of steps in the photolysis of acetone.

Nevertheless, when at Northwestern University, I found that one could apply quantum mechanics to organic molecular systems and began to investigate it in earnest. Photochemistry, at the time, was an empirical field wherein molecules seemed to react almost randomly. However, in the latter years of the 1950s, there appeared in the literature two reactions of particular interest.

Thus, Woodward and Yates elucidated the correct structure for santonin [1] and Derek Barton [2] obtained the correct structure for lumisantonin. In looking at this transformation (note eq. 1), we note a remarkable molecular reorganization. For example, the carbonyl group at C-3 now appears at C-2. The C-10 methyl group is inverted. The C-4 methyl group seemed moved to C-1.

At the time, there were no mechanisms to account for this and for the myriad known photochemical transformations. The problem was that the real reactant in a photochemical reaction is the electronic excited state of the reactant, and organic chemists were not knowledgeable in quantum mechanics. Conversely, the physical chemists were aware of the structures of some excited states, especially in the case of ketones, but were not trained in organic chemistry. It was my good fortune to have had a background in both areas.

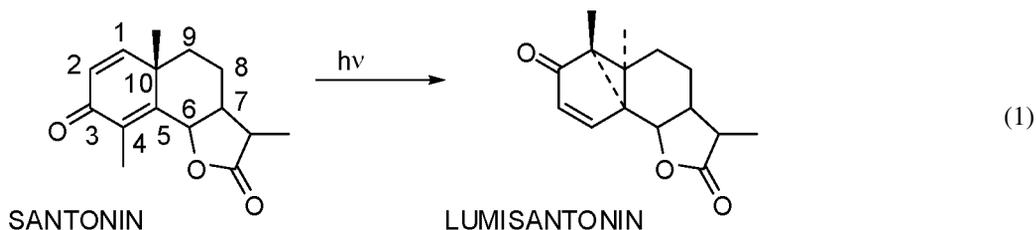
DISCUSSION

The beginning

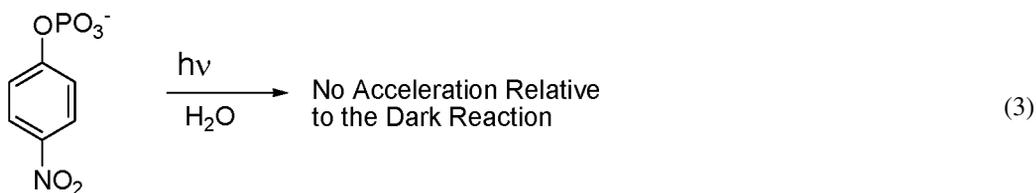
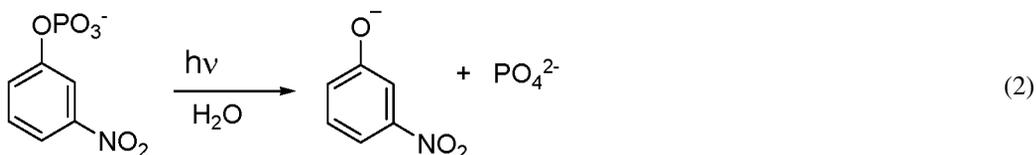
Indeed, the example that most emphasized the dilemma to me was the rearrangement of santonin to lumisantonin. As noted, the structure of santonin had been established by Woodward and Yates [1] and

*Paper based on the acceptance lecture for a 2006 Porter Medal, presented at the XXIst IUPAC Symposium on Photochemistry, 2–7 April 2006, Kyoto, Japan. Other presentations are published in this issue, pp. 2193–2359.

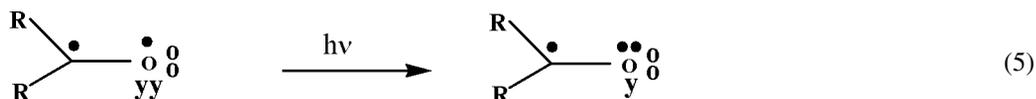
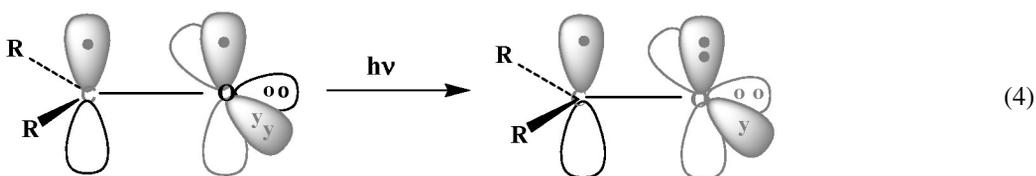
that of lumisantonin had been elucidated by Barton and his coworkers [2]. At the time, there was no mechanism available for the process in eq. 1, which was described merely as “bond crossing” [2,3]. It is seen that the reaction is particularly complex.



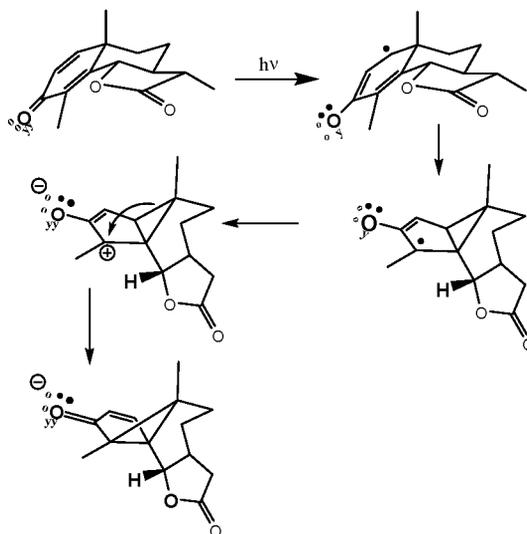
Equally puzzling was an observation by Egbert Havinga [4] concerning the solvolysis of the meta and para nitrophenyl phosphates. Of course, as we teach our undergraduates, one anticipates that the para isomer will react more rapidly due to ortho-para electron transmission. And, this was observed in the dark where the meta isomer was unreactive while the para isomer hydrolyzed reasonably rapidly. In contrast, Egbert Havinga [4] found that on irradiation, the meta isomer (eq. 2) solvolyzed rapidly while the para isomer (eq. 3) reacted no more rapidly than in the dark.



These two puzzles resulted from the fact that the true reactant in each case—that of santonin and those of the nitrophenyl phosphates—is the electronically excited state and not the ground state as pictured in eqs. 1–3. As noted in the Introduction, the physical chemists were aware of some electronic structures such as the $n\text{-}\pi^*$ excited state as depicted in eq. 4. This three-dimensional representation is somewhat cumbersome, and for purposes of quick writing, I suggested the equivalent notation of equation [5]. Here, the π system electrons are depicted as solid dots or by the usual double bonds when there are two electrons, the electrons in the p-orbital perpendicular to the paper plane are shown as y's, and the sp-hybrid electrons are the o's.

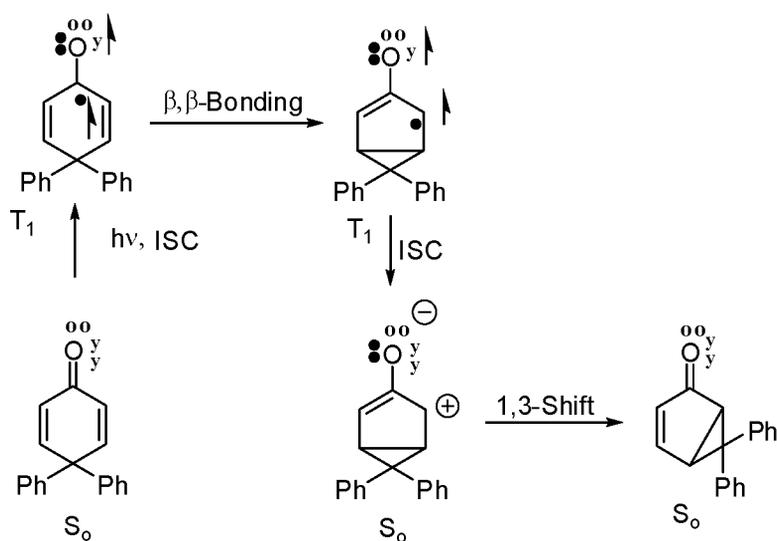


Applied to the santonin rearrangement as in Scheme 1, the mechanism leads to lumisantoinin not only with the correct structure but also with the correct stereochemistry [6].



Scheme 1 Santonin to lumisantoinin transformation in three dimensions.

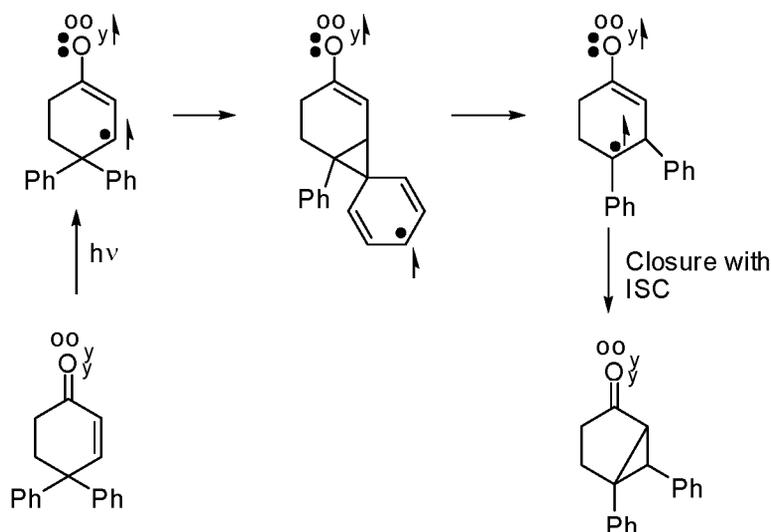
A simpler cyclohexadienone system was investigated [7] to confirm both the validity of the mechanism as well as the generality of the reaction. This is outlined in Scheme 2 and follows precisely the same mechanism utilized for the santonin rearrangement.



Scheme 2 Rearrangement of 4,4-diphenylcyclohexadienone and its mechanism.

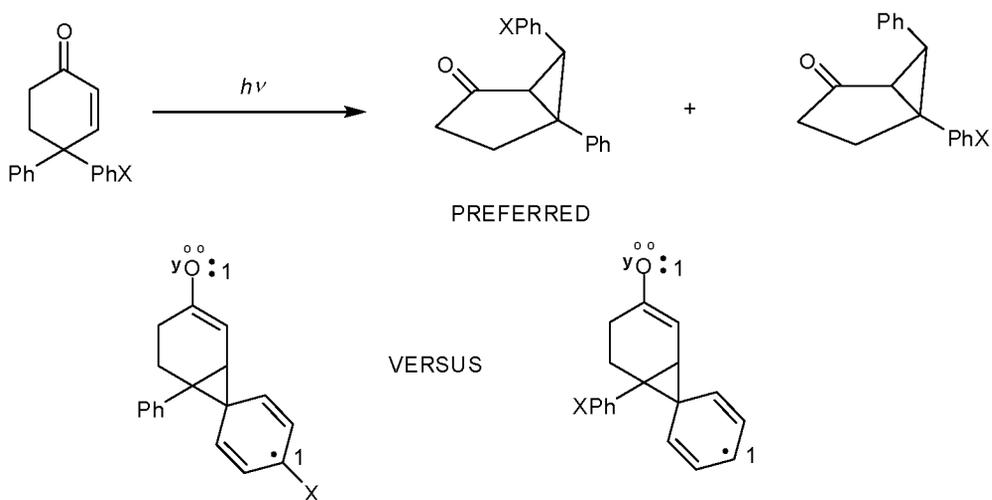
To demonstrate that the two double bonds are involved in the reaction, the photochemistry of 4,4-diphenylcyclohexenone was investigated [8a]. In this case, a phenyl group migrated, giving what I

have termed the "Type B" rearrangement and which now is a very common reaction. The mechanism is depicted in Scheme 3.



Scheme 3 Type B rearrangement of cyclohexenones.

When one of the phenyl groups is substituted in the para position with a cyano or a methoxy group, that aryl group migrates in preference. This clearly results from the extra electron delocalization in the bridged intermediate as depicted in Scheme 4.



X = CN or MeO

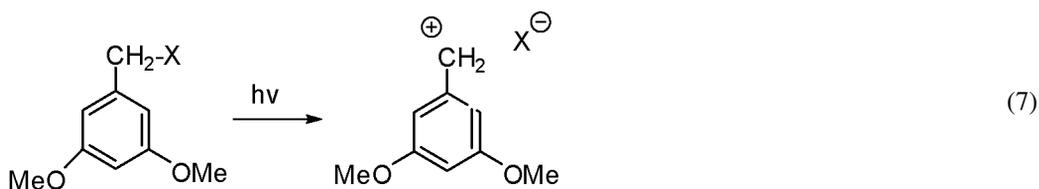
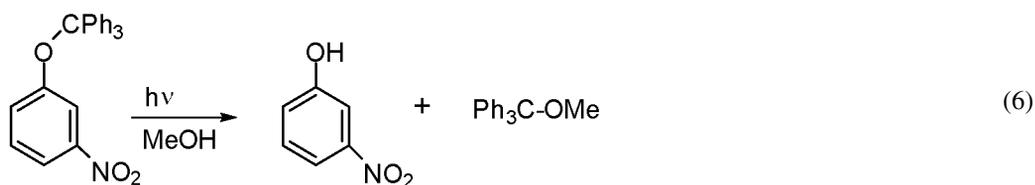
Scheme 4 Regioselectivity in the Type B rearrangement of cyclohexenones.

Parallel application of the $n-\pi^*$ structure to a series of ketone reactants led to mechanisms for a large group of photochemical reactions known at the time [5]. Among the examples were the Norrish

type I, the Norrish type II, the Paterno–Büchi reaction, α -expulsion in haloketones, and the rearrangement of epoxyketones.

In those early days, the computing available was with an IBM-1604 and Hückel methodology. Nevertheless, it proved possible to understand some reactivity on the basis of calculated bond orders and electron densities. One example was the $n\text{-}\pi^*$ excited state of 2,5-cyclohexadienones, which uniquely had a positive β,β -bond order, thus accounting for the first step after electronic excitation in Scheme 1 [9,10].

In the case of the remarkable behavior of the meta and para phenylphosphates described by Egbert Havinga, I was able to generalize the reactivity of meta substituted derivatives. Thus, in eq. 6 irradiation of the meta-nitrophenyl trityl ether led to loss of the meta-nitrophenolate and formation of the trityl cation which could be captured nucleophilically (note eq. 6) [11]. The mirror image situation was uncovered in the case of 3,5-dimethoxybenzyl derivatives as depicted in eq. 7. I then termed this the “meta effect” since in the excited state, transmission of electron density occurs between meta positions in contrast to ground-state chemistry where ortho-para transmission is normal.

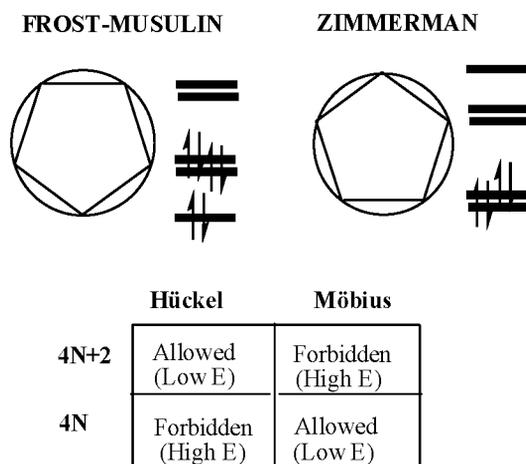


In 1966, it was noted [13] that there are Möbius systems both in transition states and in molecular systems in general. A mnemonic was suggested as shown in Scheme 5 which permits easy determination of the molecular orbital (MO) energy levels. The mnemonic is similar to the Frost–Musulin one [14] except that a polygon side is placed at the bottom of the circle rather than a vertex. This is shown in Scheme 5. Möbius systems consist of cyclic arrays of basis orbitals with an odd-number of sign inversions around the cycle. This contrasts with the common Hückel systems with zero or an even number of such inversions. Thus, these systems follow, respectively, the $4N$ and $4N+2$ rules (note the Table at the end of Scheme 5). The method provided a simple alternative to the 1965 Woodward–Hoffmann treatment [15]. The use of nodal parity is found again in the 1970 Woodward–Hoffmann text [16] where bonds rather than local orbitals are used as the basis.

The use of degeneracies obtained by the Möbius–Hückel mnemonic permits facile drawing of reaction correlation diagrams, since for each degeneracy there is a crossing of MOs. Thus, when all the bonding MOs of a reactant are occupied and there is a nonbonding degeneracy, the reaction is forbidden.

Interestingly, even earlier [17] the first organic correlations diagram was presented. In this general treatment not based on symmetry, it was noted that when occupied bonding MOs become antibonding, the reaction is impeded. A correspondence was noted between the degree of antibonding character and inhibition of the reaction rate.

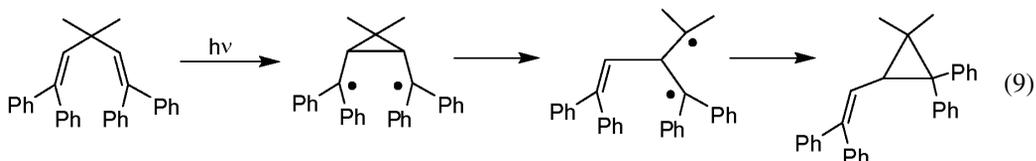
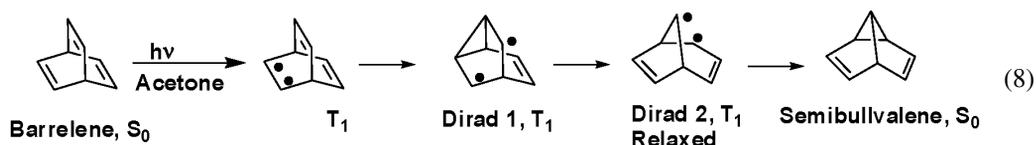
It is noted that Möbius systems occur in other than pericyclic reactions. For example, in barrelene, the π MOs of the three ethylenic bonds form a triangular, Möbius array; and the MO energies are split in -1 and $+2$ fashion.



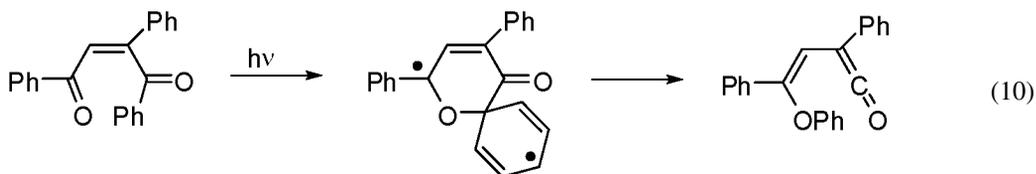
Scheme 5 Wisconsin Möbius–Hückel mnemonic (right) for Möbius systems contrasted with the Frost–Musulin one for Hückel systems.

The interim years

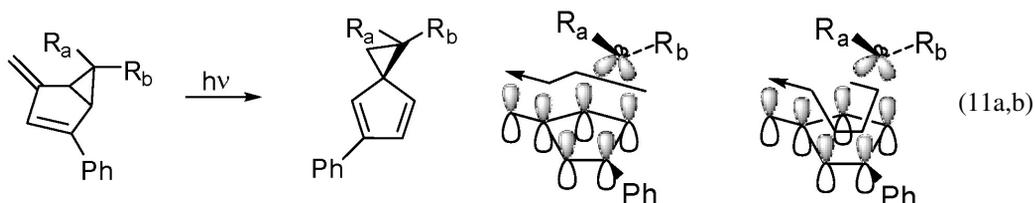
Over the time leading to about 1985, a rather large number of new photochemical reactions and phenomena were uncovered, much more than can be included in this description of my lecture. Among these was the di- π -methane rearrangement [18] (eqs. 8 and 9). The di- π -methane rearrangement was originally encountered when we had synthesized barrelene and then found its photolysis to give a C_8H_8 isomer which we termed semibullvalene, a molecule which was found to undergo an exceedingly rapid degenerate Cope rearrangement [18a,b]. The mechanism of the barrelene to semibullvalene rearrangement is given in eq. 8. Once the mechanism was recognized, it was ascertained that the reaction was more general, with the reactant requiring only two π groups bonded to an sp^3 -hybridized carbon as in eq. 9. Also, soon thereafter, independent syntheses of semibullvalene were discovered [19a,b]. One involved the photochemistry of cyclooctatetraene [19a].



A reaction whose mechanism was a bit obscure had been the rearrangement of dibenzoyl ethylenes, and the mechanism was determined as that in eq. 10 [20].



A somewhat bizarre reaction that developed was the bicycle rearrangement depicted in eq. 11a [21]. The major product results from a counter-clockwise bicycling of the carbon bearing groups R_a and R_b as shown. However, some clockwise bicycling as shown in eq. 11b on the far right leads to the reverse stereoisomer.



Recent years

In recent years, we have focused on solid-state organic photochemistry, a “Delta-Density” theoretical treatment capable of predicting the proclivity of bond fission and bond formation in the Franck–Condon vertical excited state, exploration of excited-state hypersurfaces for conical intersections involved in reactions, detailed inspection of the factors leading to our “meta-effect”, dissection of intersystem crossing into local molecular contributions, discovery of a tri- π -methane rearrangement, and a study of some unique heterocyclic reactions.

In solid-state photochemistry, it had been recognized for a century that irradiation of reactants in the crystalline state most often leads to photoproducts which differ from those observed for solution photolysis. In the case of unimolecular reactions (e.g., rearrangements), no really satisfactory theory had been advanced. For individual cases, X-ray analysis of a reactant often would reveal some group too encumbered to undergo the solution reaction. However, the idea of Cohen and Schmidt was most satisfying [22]. They suggested that each reacting molecule is surrounded by neighbors, and the neighbors constitute an irregularly shaped cavity. Not all transition states can fit into this cavity. The concept, although brilliant, was qualitative.

Since in our research group we do our own X-ray analyses, I realized that for each crystal we knew the coordinates of each atom of the neighboring molecules and thus knew the precise shape of the cavity. This led to a publication entitled “The Quantitative Cohen-Schmidt Cavity” [23]. The X-ray crystal structure was truncated. Then, a single central reactant molecule was replaced in separate tests by all possible first intermediates. In Fig. 1, the reactant **R** selected is shown as the bold **R** and its transformation product **I** is again shown as bold. **I** is selected, first, as the first reaction intermediate involved in the solution reaction, next as the intermediate involved in the observed solid-state reaction, then as an intermediate involved in any observed side-reaction, and finally as any reasonable intermediate which might have been anticipated in the reaction. Invariably, the intermediate which “fits” best in the cavity was the one observed experimentally as affording photoproduct. “Fit” was determined as minimal overlap with the neighboring molecules and also with minimum energy as determined with molecular mechanics. A serious problem is that molecular mechanics measures only steric effects and ignores electronic factors.

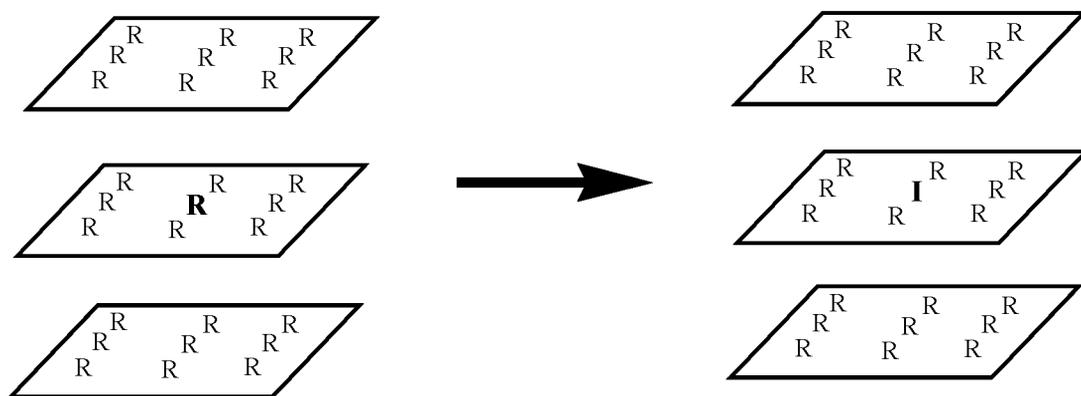


Fig. 1 Representation of a reactant cavity with the reactant **R** (bold) molecule R then replaced by a first intermediate **I** (bold).

Thus, a second approach was devised [24]. This is shown in Fig. 2 where all but the closest neighboring atoms were computationally annihilated. These are at the vertices of the polyhedron surrounding the reacting species shown in the center. These atoms had “dangling” free-valencies, a problem which was obviated by converting the hydrogens to heliums and the other atoms to neons. The inert gas atoms take minimal ab initio computation time and permit the entirety to be subjected to a CASSCF ab initio Gaussian computation [25].

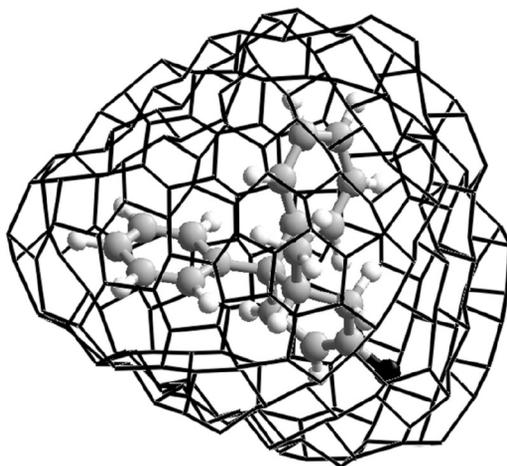
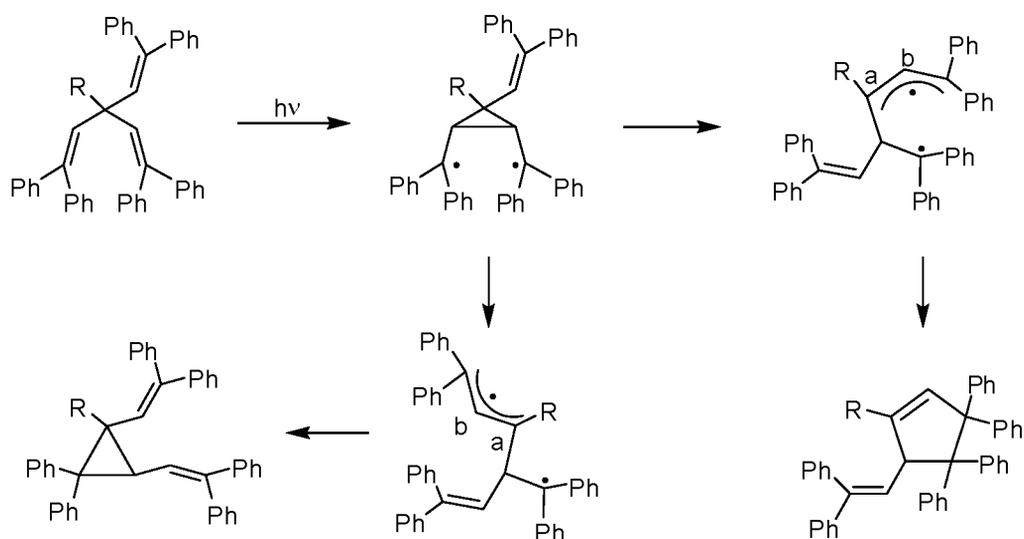


Fig. 2 Perspective view of a quantitative reaction cavity with a central reacting molecule (5-methyl-4,4-diphenylcyclohexenone).

Interestingly, the same predictions of preference of reaction courses were observed. Of course, the ab initio energies obtained differed from those observed using molecular mechanics. The important conclusion, however, is that control of unimolecular reactivity is primarily steric and not electronic. If a transition state cannot fit into the quantitative cavity, it does not matter how good electron delocalization is.



Scheme 7 Tri- π -methane rearrangement.

CONCLUSION

My conclusion would have been put into the Acknowledgment. However, a more extended statement is required. Thus, all of the research described above would not have been possible without the participation of the most remarkable research group of former students. I don't know what I did to deserve all of these but somehow they joined me in what has been a very exciting set of decades. There have been 86 of them who liked what they did enough that they, themselves, became professors. To all of my former students I can only offer appreciation and thanks.

ACKNOWLEDGMENT

Support of our basic research by NSF over the decades is gratefully acknowledged.

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