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Photochemical Reactions as a Tool in Organic Syntheses

Photochemical methods serve as a useful and powerful complement to conventional synthetic methods.

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A little more than a decade ago a vigorous interest in the photoreactions of organic molecules began to develop (*1*). That initial interest was followed by a tremendous research effort in the area of photochemical mechanisms (*2*) and was paralleled by remarkable and rapid technical breakthroughs in the generation and control of light, especially in the areas of pulsed excitation which allow the study of dynamic processes with duration as short 10^{-12} second (*3*). The new respectability, which resulted from the development of a mechanistic framework for photoreactions, encouraged synthetic chemists, who may have originally viewed photoreactions as nonselective "cryptopyrolysis," to explore the possible uses of photochemical methods in designing the synthesis of organic molecules.

This article is concerned with the use of photochemical reactions as key steps in the strategy of the laboratory synthesis of organic molecules. We demonstrate that synthetic selectivity and control are common in many photoreactions and that some of the unique aspects of the photochemical method allow unique opportunities for syntheses. Indeed, in the area of generation of reactive molecules possessing high energy content, photoreactions provide avenues for syntheses that are unparalleled by conventional synthetic methods.

Some important aspects of photochemical reactions. From the standpoint of synthesis, a photon may be considered as a reagent which "reacts" with a molecule as a result of absorption. The analogy of the photon as a reagent is actually an effective concept in that the act of light absorption transforms a ground state molecule M into an electronically excited molecule M*. The physical and chemical properties of M and M* may drastically differ one from another. For example, acetone in its ground state is indefinitely stable in alcoholic solvent, but irradiation of an alcoholic solution of acetone leads to an efficient photoreaction. In effect, we can view the electronically excited molecule M* as an electronic isomer of M; that is, the two species are related by having the same molecular composition and structural formulas but differ in the electronic arrangement.

Guidelines to understanding photoreactions. Organic photochemistry has made extraordinary advances as a science during the last decade. In part, the explosion of research in this area has been triggered by technicological developments that have provided invaluable and powerful tools for the study of electronically excited states. Perhaps even more important, however, was the rapid development of an intellectual fabric to hold the discipline together and to guide experimental design. Just a few concepts that differ a bit from those encountered in "conventional thermal chemistry" are required to understand organic photochemical processes.

In usual thermal synthetic methods of organic chemistry, heat provides the activation required to cause reaction. Selection of the reaction path is obtained by appropriate choice of variables, such as starting substrate structure, reagents, and reaction conditions (for example, solvent, catalyst, and concentrations). In a photoreaction, the absorption of light provides most and sometimes all of the activation required to initiate reaction. In addition to the usual variables in thermal reactions, photochemical reactions possess several additional possibilities for controlling reaction selectivity, the most important of which is the strategy of specific excitation of a particular atom or group of atoms in a molecule. This selectivity, when coupled with (i) the possibility of photoexcitation under very mild reaction conditions (that is, very low temperatures), (ii) the common observation that many photoreactions proceed in good to acceptable yield, and (iii) some simple but powerful ideas for predicting photoreactions make photochemistry a powerful, valuable, and versatile tool in the synthesis of organic molecules.

Theory of organic photoreactions: the three state principle. The following hypotheses provide a simple, powerful working theory of organic photoreactions: (i) light absorption corresponds to the excitation of an electron from a bonding or nonbonding orbital into the lowest unfilled orbital available to the molecule; (ii) the molecular state which results from excitation of an electron rearranges very rapidly to the state corresponding to the lowest energy (mono) excited electronic configuration; and (iii) each excited electronic configuration may exist as a singlet state (all electron spins are paired) or as a triplet state (two electron spins are parallel).

The consequences of these hypotheses

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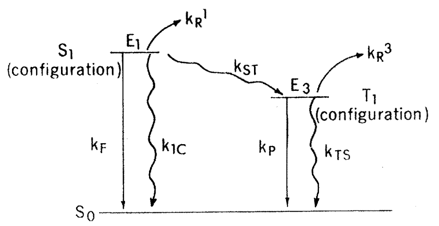


Fig. 1. A shorthand energy diagram. The various k's represent the following rate constants: k_F, fluorescence; k_{IC}, radiationless deactivation of singlet; k_R^1, chemical reaction from singlet; k_P, phosphorescence; k_{TS}, radiationless decay from triplet; k_{ST}, intersystem crossing; and k_R^3, chemical reactions from triplet.

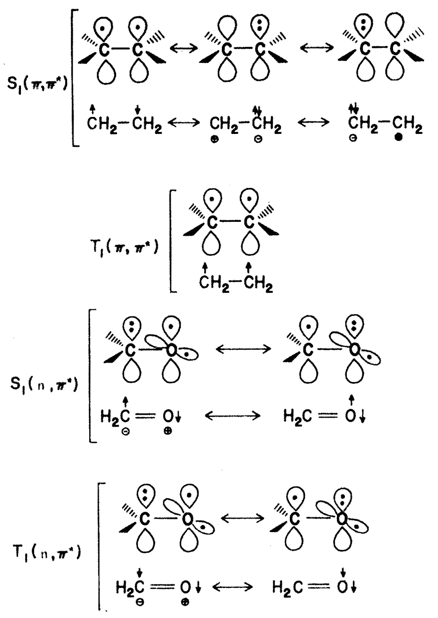
are concisely summarized in an electronic energy diagram (Fig. 1). In this diagram the energy of the lowest excited singlet state (S_1) is shown relative to the lowest energy triplet state (T_1) and the ground (usually singlet) state (S_0). In addition to energy, both S_1 and T_1 possess a characteristic electronic configuration (which determines chemical reactivity) and lifetime (which limits reaction efficiency). The configuration of a state determines, in the main, the photoreactions that are possible for the state, but the lifetime determines whether these reactions are efficient or can occur at all.

In general, S_1 states are shorter lived (τ is the lifetime) than T_1 states ($\tau_{S_1} = 10^{-7}$ to 10^{-11} second and $\tau_{T_1} = 10^{-3}$ to 10^{-6} second, respectively) and have higher energies (E) [$E(S_1) = 100 - 50$ kcal/mole and $E(T_1) = 80$ to 30 kcal/mole, respectively]. For comparison the strongest single bonds in molecules have dissociation energies of 100 kcal/mole (for example, C-H and O-H bonds) and the weakest single bonds have dissociation energies of about 35 kcal/mole (for example, O-O bonds). The dissociation energies of most other bonds in organic molecules fall in the range of 80 to 60 kcal/mole.

Reactivity and efficiency principles. The state configuration approximation. An important generalization is the state configuration approximation. This principle assumes that S_1 or T_1 (states) can be adequately described in terms of two electrons involved in the $S_0 \rightarrow S_1$ or $S_0 \rightarrow T_1$ processes, which determine a configuration of electrons for each state. The chemical reactivity of the S_1 and T_1 states are determined by the specific electronic configurations that can usually be considered to be of either the n,π^* or π,π^* type (as discussed below). The efficiencies of reactions of S_1 and T_1 are determined not only by proclivity toward reaction, but also by lifetimes, since the efficiency of reaction represents a competition between the rate of reaction and other means of decay. The competition is measured by the quantum efficiency of a reaction, which relates the number of product molecules produced per quantum of light absorbed. This quantity is determined by the ratio of the reaction rate and competing excited state decay rates. Fortunately, many photochemical reactions with low quantum efficiency still give a high chemical yield of product. Since S_1 is usually much shorter lived than T_1 we expect that S_1 will not efficiently participate in bimolecular reactions, since the reaction of S_1 in a bimolecular process will require very high concentrations of reactant in order to compete with unimolecular decay of S_1. Likewise, we expect that the longer lived T_1 may participate efficiently in both unimolecular and bimolecular reactions.

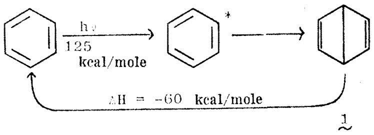
Pathways of molecular electronic excitation. Direct photoexcitation and photosensitization. It is an important fact that ordinary absorption of light serves to populate only S_1 to any significant extent. Thus, population of T_1 requires an indirect pathway. Two methods for population of T_1 are available: (i) an intramolecular pathway, namely intersystem crossing, an $S_1 \rightarrow T_1$ radiationless interconversion (that is, no light is emitted) and (ii) an intermolecular pathway, namely triplet-triplet energy transfer, a radiationless transfer of energy from one molecule to another. The latter is an example of photosensitization and is required when the substrate molecule possesses an inherently inefficient $S_1 \rightarrow T_1$ pathway and can also be used to selectively quench T_1 photochemistry. Table 1 lists some typical chromophores with relevance to the processes discussed above. A guiding principle for the use of triplet-triplet photosensitization (*4*) is the rule that the rate of energy transfer from one triplet to another is mainly determined by energetics, with exothermic energy transfer (triplet of donor > triplet of acceptor) occurring readily.

Utilization of absorbed light energy: energy capture, exchange, storage, and release. One may view photoreactions in terms of a sequence of energy interchanges or exchanges. First, the energy of a photon is captured by light absorption, next the initial energy of the absorbed photon is exchanged for vibrational and electronic energy until the S_1 or T_1 state is reached. The electronic excitation energy of S_1 and T_1 may then be exchanged for bond energies and be stored temporarily in the form of a high energy reactive intermediate or released as a stable isolable product is formed. The latter may be a molecule of high energy content which has itself stored a major fraction of the electronic excitation energy of S_1 or T_1 as bond energy.



Scheme 1

As an example of these ideas, consider the photochemical conversion of benzene (*5*) into bicyclo[2.2.0]hexadiene (Dewar benzene) **1** (Eq. 1). A high energy photon of, say, 125 kcal/mole may be absorbed by benzene to produce a reactive singlet state of benzene. Some of this original photon energy is lost to the environment as vibrational relaxation energy (heat), but a sizable fraction is stored in the strain energy of the product. Indeed, the heat of reaction for rearrangement of Dewar benzene to benzene is exothermic by about − 60 kcal/mole (*6*).



(1)

This feature of energy exchange represents a major theoretical distinction between conventional "thermal" reactions and photochemical reactions. In a sequence of thermal reactions, the thermodynamic requirement for an overall free energy decrease provides a severe limitation on the energy content of molecules which can be synthesized. In effect, energy must be stored in stages or as intermediates until the high energy molecule is constructed, that is, work must proceed uphill energetically. As the molecule becomes more energetic, usually the reaction conditions must become milder and the reaction temperature must become lower.

In a photochemical reaction, however, the general energy sequence is reversed. We start with a molecule that possesses an energy content equivalent to that of the absorbed photon and from this point the energy of the system drops in value. Thus, the excited molecule may explore reactions and generate molecules whose energies are well above those of the transition states for conventional thermal chemistry of the substrate. It is virtually impossible to prepare Dewar benzene from benzene by any purely thermal sequence because of the very unfavorable endothermicity of the reaction.

Important excited state types: π,π^* and n,π^* states. It is possible to correlate a wide range of photoreactions on the basis of classification by (i) excited state configuration and (ii) excited state multiplicity. In general, most excited configurations can be classified as π,π^* in nature (that is, the two "key electrons" are located above and below a molecular plane) or n,π^* in nature (that is, the n electron is located in the molecular plane and the π^* electron is located above and below a molecular plane).

We may exemplify (scheme 1) these classifications in terms of important resonance structures for a typical π,π^* state and a typical n,π^* state.

Classification: photoreactions that make, break, or isomerize carbon-carbon bonds. The syntheses of organic molecules may be considered to require two major kinds of reactions: those which make, break, or isomerize carbon-carbon bonds and those which interconvert functional groups. We will consider here the use of photochemistry to effect reactions in the first category.

Three types of conceptual frameworks for classification may be employed to discuss photoreactions. First, we can employ a purely phenomenological classification based on reaction types. This treatment recognizes that only a small set of truly distinct reaction types occur and that the overwhelming majority of photoreactions can be successfully classified in terms of this set. Second, photoreactions may be considered in terms of reactions of chromophores, the light absorbing units of molecules. This attitude uses some theory to sort out the ideas of what constitutes a chromophore and what its photochemistry is likely to be. Within this theoretical framework, photoreactions may be classified in terms of the typical reactions of each chromophore. Finally, a third approach considers photoreaction mechanisms and classifies reactions of individual chromophores on the basis of a small set of general mechanisms.

Table 1. Dynamic and energetic data for some organic molecules at 25°C.

Molecule	E_1* (kcal/mole)	E_3† (kcal/mole)	k_{ST}‡ (sec^{-1})	k_{TS}§ (sec^{-1})
Benzene	115	85	10^7	10^6
Naphthalene	90	61	10^7	10^6
1-Fluoronaphthalene	89	60	10^7	?
1-Chloronaphthalene	89	59	10^8	?
1-Bromonaphthalene	89	59	10^9	?
1-Iodonaphthalene	89	59	10^{10}	?
Anthracene	76	42	10^8	10^4
Benzophenone	75	69	10^{10}	10^5
Biacetyl	62	56	10^8	10^4
Acetone	84	78	10^8	10^6

* Singlet energy. † Triplet energy. ‡ Rate constant for conversion of singlet to triplet, order of magnitude only. This rate usually limits singlet lifetime in solution. § Rate constant for pseudo unimolecular decay of triplet to ground state in solution. Strongly solvent dependent; order of magnitude only.

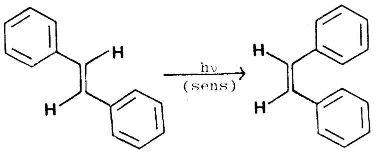
Classification by reaction types. Although an interplay should and will occur among the three approaches—from the standpoint of photochemistry as a synthetic tool—the concepts of reaction types is probably the most useful. For example, almost all known photoreactions can be classified in terms of six types: *cis,trans* isomerization, fragmentation, reductive additions to multiple bonds, electrocyclic reactions, sigmatropic reactions, and cycloaddition reactions.

Of this group, only reductive addition to multiple bonds and cycloaddition reactions are intermolecular in the sense that two components are involved and that one component in the reaction is electronically excited and the other is in its ground state. The other reaction types are fundamentally intramolecular in nature.

From the standpoint of classification by reaction types we can now proceed to add new types of information that will make our system of thought more useful from the standpoint of a tool in synthesis. These include (i) realization of the fundamental differences between photoreactions and thermal reactions, so as to better define the advantages and limitations of the method; (ii) elucidation of the classes of molecular structural types that are best synthesized by photochemical methods, and (iii) evaluation of synthetic strategies by consideration of known and probable photochemical mechanisms.

Photochemical cis,trans *isomerization.* Photochemical methods for effecting *cis,trans* interconversions offer several variables for controlling the composition of the product mixture. (i) Different absorption spectra of the *cis* and *trans* isomer allow the possibility of "pumping" of light specifically into one isomer and thereby driving the isomerization toward the nonabsorbing component; (ii) photosensitization allows the possibility of selectively transferring energy to one of the two isomers and thereby "drive" the isomerization toward the isomer which is least affected by the photosensitizer; (iii) *cis* to *trans* isomerization of cyclic olefins (of ring size less than nine carbons) results in generation of a reactive, strained *trans*-cycloalkene which can be used as a reagent in syntheses.

The photochemical interconversion of the stilbenes provides an example of methods (i) and (ii). Both direct excitation (*7*) and photosensitized excitation (*8*) can be employed to convert the thermodynamically more stable *trans*-stilbene into *cis*-stilbene (Eq. 2).

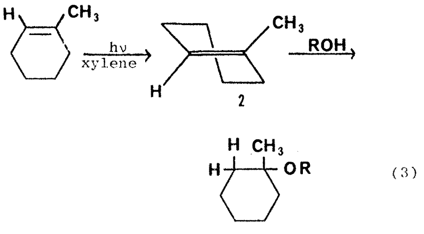


(2)

(If a reaction occurs by *both* direct *and* photosensitized excitation, we employ a convention of placing parentheses about *Sens*. If the reaction only occurs by photosensitization, the parentheses are not included.)

An example of method (iii) is the

photosensitized addition of protic solvent to cycloalkenes (*9*). The xylene sensitized addition of methanol to methylcyclohexene (Eq. 3) is believed



(3)

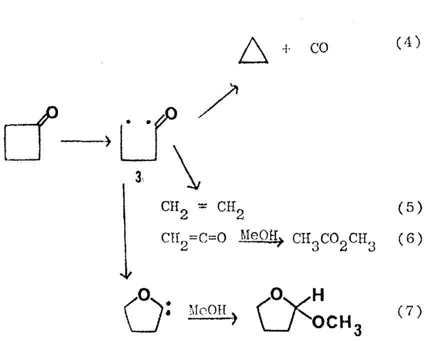
to involve intermediacy of an exceedingly strained *trans*-cyclohexene (**2**) which is then attacked by solvent (*10*).

In some cases the highly strained *trans* intermediate may be isolated or detected spectroscopically (*11*).

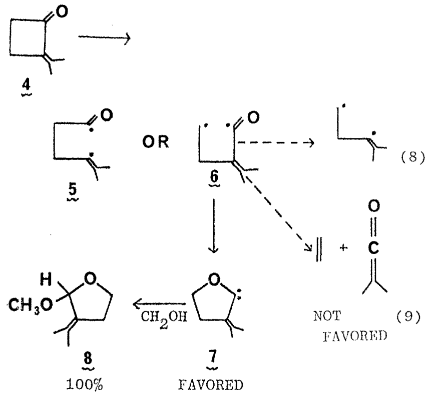
Photochemical fragmentations. Production of carbon radicals, diradicals, carbenes, and other reactive intermediates. Relatively weak bonds to carbon, dissociation energies (E_d) less than 70 kcal/mole, can often be cleaved by photoexcitation. For example, the cleavage of carbon-iodine ($E_d \simeq 70$) bonds results in formation of carbon radicals (*12*) that are very reactive toward hydrogen abstraction or addition to form a carbon-carbon bond. The photoexcitation and loss of nitrogen from cyclic azo compounds is thought to generate a biradical (*13*). Photoexcitation and loss of nitrogen from diazo compounds (*14*) generates carbenes. Many analogous photoreactions that produce carbon radicals, biradicals, or carbenes have been exploited for use in syntheses.

From the notions of modern photochemical theory, some useful syntheses involving photofragmentation can be designed. The idea of high energy intermediates that intervene between the electronically excited molecule and the isolated product is of great utility in developing a strategy for application of photoreactions.

In the way of an example, consider the photochemical reactions of cyclobutanone in a solvent such as methanol (Eqs. 4 to 7). The isolated products are all logically derived from one initial reactive intermediate, the 1,4-biradical **3**, formed by cleavage of the carbon-carbon bond position α to the carbonyl group of cyclobutanone (*15, 16*). Since a mix of reaction products is obtained, we might conclude that the reaction will have little synthetic value. However, consideration of the type of substituents which will direct **3** more selectively toward one of the products enhances the synthetic power of the general class of photoreactions of cyclobutanones. For example, consider the isopropylidene **4**. If we hypothesize that a biradical is formed upon photoexcitation and α-cleavage of **4**, we expect that (i) since the biradical **6** will be more stable than **5**, the former will be formed preferentially and (ii) since decarbonylation and cycloelimination both require cleavage of an sp^2-sp^2 bond, these processes should be less favored [relative to the reactions of the model biradical (**3**)] than ring expansion to the carbene **7**. In fact **8**, the carbene adduct of **7** and methanol, is formed in quantitative yield.

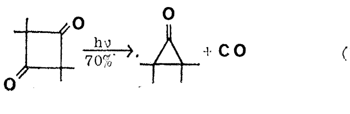


(4)
(5)
(6)
(7)

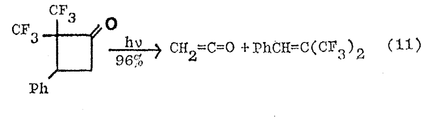


(8)
(9)

After further consideration of the expected chemistry of 1,4-biradicals related to **3**, appropriate structural substitution allows decarbonylation (Eq. 10) or cycloelimination (Eq. 11) to



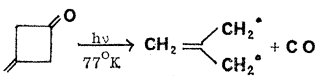
(10)



$CH_2{=}C{=}O + PhCH{=}C(CF_3)_2$ (11)

become the major reaction pathways (*17, 18*).

Since photoreactions can be induced to occur in solid matrices at low temperatures, very reactive intermediates can be generated and "stabilized" toward secondary reactions. Exquisite examples of this method are provided by a number of low temperature photofragmentations in matrices which have generated (*14, 19, 20*) the theoretically interesting molecules trimethylene methane (Eq. 12) (*21*), benzene (Eq. 13), and a dimethyl α-lactone (Eq. 14). It is also possible to generate and stabilize carbenes (Eq. 15) under these conditions (*22*).



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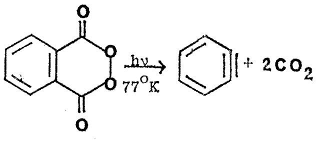

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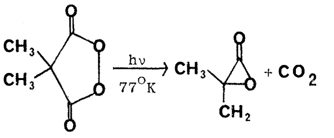
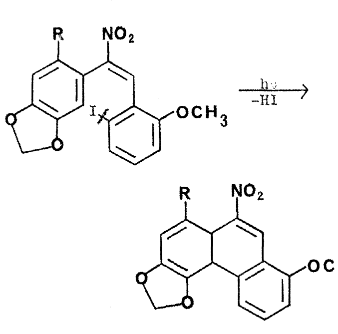


(14)

$$PhC{=}N_2 \xrightarrow[77^\circ K]{h\nu} Ph_2C: + N_2 \qquad (15)$$

Another example of a photochemical cleavage is Eq. 16. Cleavage of the carbon-iodine bond results in generation of a phenyl radical (*12*) which attacks the ortho position of a neighboring phenyl group to complete a bond forming cyclization, and serve as the key step in the synthesis (*23*) of aristolochic acid, **9**, a tumor inhibitor. Irradiation of the cyclic azo compound, **10**, results in loss of nitrogen (*24*) and probable formation of a biradical which closes in part to the remarkable benzene isomer prismane (Eq. 17). Photolysis of the diazo compound **11** results in loss of nitrogen and generation of a carbene which rearranges quantitatively to the β-lactam **12**, a structural type commonly encountered in penicillins and cephalosporins (*25*).



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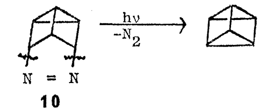

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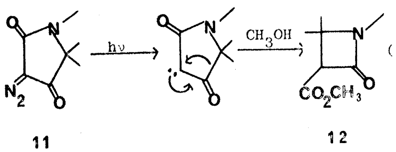
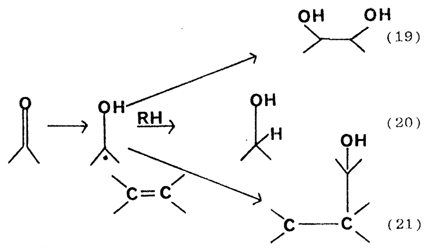
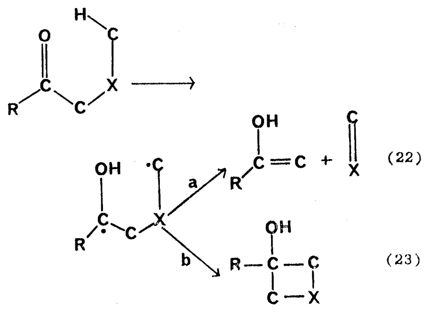


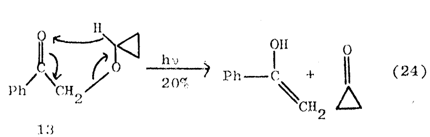
11 **12**

Photochemical reductive addition to multiple bonds. Intermolecular hydrogen abstraction reactions of carbonyl compounds. Let us consider the n,π^* triplet of ketones, which are capable of undergoing synthetically useful inter- and intramolecular hydrogen abstraction reactions (*26*). These reactions convert the ketone into a ketyl radical which can then react further. For example, depending on the reaction conditions, the product of the initial hydrogen abstraction may be an alcohol, a pinacol, or an adduct to a ketyl radical trap such as an unsaturated molecule. Thus, this reaction is a means of effecting carbonyl reduction and carbon-carbon bond formation (Eqs. 19–21).



Carbonyl compounds possessing a hydrogen capable of forming a six-membered transition state for hydrogen abstraction by the oxygen are capable of forming 1,4-biradicals which can then either fragment (Eq. 22) or cyclize (Eq. 23). This intramolecular hydrogen abstraction has two immediate synthetic possibilities: (i) as a method of fragmenting bonds or (ii) as a method of making small rings. These processes are known as type 2 cleavage and cyclization reactions of ketones. This reaction usually occurs to the exclusion of abstractions involving smaller or larger cyclic transition states, except in special cases (as discussed below). The photochemical synthesis of cyclopropanone (*27*) from **13** (Eq. 24) and of **15** (*28*) from **14** (Eq. 25) are examples of these methods.





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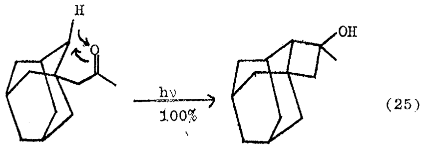
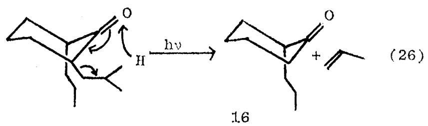


14 **15**

The regio-specificity of the hydrogen abstraction step can be ascribed to the radical like half-filled n-orbital of the n,π^* state which shows preferred reactivity at the "edges" rather than the "faces" of the carbonyl function. As a result of this selectivity the 2,6-di-*n*-propylcyclohexanone undergoes exclusive cleavage (*29*) of the equatorial side chain and results in formation of the axial substituted cyclohexanone **16**.



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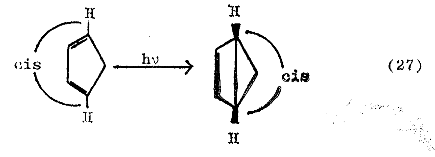
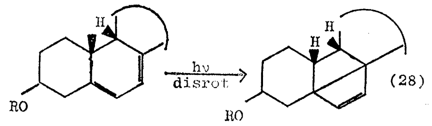
An ingenious extension of the intramolecular hydrogen abstraction has been developed into a method of remote functionalization (see below).

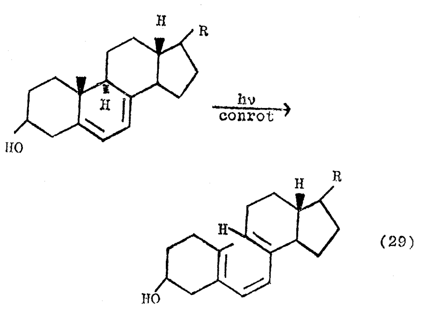
Photochemical electrocyclic and sigmatropic reactions. The majority of known synthetically useful photoreactions involve triplet states. This situation arises from the higher general efficiency of triplet reactions relative to singlet reactions and is usually the result of the shorter singlet lifetime rather than lower singlet reactivity toward reaction. Electrocyclic reactions and sigmatropic reactions (*30*) provide a major exception to the above generalization because many singlet states possess a rate of electrocyclic and sigmatropic reactions which is competitive with other singlet deactivation modes and most triplet states are not reactive toward concerted electrocyclic and sigmatropic processes. A simple hypothesis which makes the reactivity difference between singlet and triplet understandable is that electrocyclic and sigmatropic reactions are concerted and therefore capable of proceeding smoothly from reactant (singlet) to product singlet. The high stereospecificity of photochemical electrocyclic and sigmatropic reactions is further evidence in support of this hypothesis.

The following simple rule of reaction stereospecificity derived from orbital symmetry consideration (*30*) holds almost without exception: Photoinitiated electrocyclic reactions involving $4n$ electrons proceed with preservation of stereochemistry at the reaction termini (disrotatory bond formation), whereas photoinitiated electrocyclic reactions involving $4n + 2$ electrons proceed with inversion of stereochemistry at the reaction termini (conrotatory bond formation).

As an example (*31*), the four-electron electrocyclic ring closure of cyclic 1,3-dienes to cyclobutenes proceeds smoothly because configurational preservation (disrotation) at the reaction termini allows formation of a *cis*-fused cyclobutene (Eq. 27). On the other hand, the six-electron ($4n + 2$) electrocyclic ring closure or opening of 1,3-cyclohexadienes must occur with stereochemical inversion (conrotation) at the reaction termini (*30*). Such a process is energetically feasible in the absence of structure restraints at the reaction termini. Consider, however, the contrasting behavior (Eqs. 28 and 29) of isopyrocalciferol (methyl and hydrogen at reaction termini *cis*) and ergosterol (methyl and hydrogen at the reaction termini *trans*). In the former case, a photoinduced four-electron electrocyclic ring closure to form a strained [2.2.0]bicyclohexene system occurs (*32*) to the exclusion of the apparently strain-releasing six-electron electrocyclic ring opening to form a 1,3-hexatriene. On the other hand, the latter reaction is

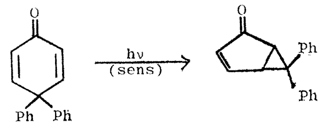






observed (*33*) in the case of ergosterol. The above rule for photoinduced electrocyclic reactions makes these results understandable since a six-electron ring of isopyrocalciferol must proceed with stereochemical inversion at a reaction terminus, thereby generating a *trans* double bond in a cyclohexene ring. Apparently the activation energy required for such a process is larger than that for the four-electron ring closure. In the case of ergosterol, however, the conrotatory six-electron ring opening transforms a *trans* stereochemistry at the reaction termini to a strain-free *cis*-stereochemistry in the 1,3,5-hexatriene product.

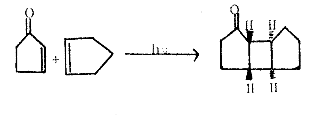
Of the various photochemical sigmatropic shifts which have been discovered over the last several years, the [1,2] shift to yield a cyclopropane probably has the greatest synthetic utility. This reaction is particularly ubiquitous in 1,4-conjugated systems, and such cases have been dubbed "di-π-methane rearrangements" (*34*). Most reported sigmatropic shifts appear to originate from singlet states, but [1,2] sigmatropic shifts are known to also proceed via triplets. The now "classical" photorearrangements (*35*) of 2,5-cyclohexadienones to bicyclo[3.1.0]hexenones (Eq. 30) are examples of [1,2] shifts.



(30)

Photochemical cycloadditions and cycloeliminations. The 2+2 photocycloaddition of unsaturated molecules is one of the most general and synthetically useful of all photoreactions (*36*). This reaction has been exploited as the key carbon-carbon bond–forming step in a large number of synthetic efforts. This photoreaction rivals, in its synthetic aspects, the thermal 4+2 cycloaddition, the venerable Diels-Alder reaction. The intramolecular variation of the photochemical 2+2 cycloaddition is usually more reliable than the intermolecular pathway. As in the case of most photoreactions, this generalization probably derives from the fairly short lifetimes of the electronically excited states of unsaturated compounds, rather than from a lack of reactivity toward cycloaddition.

The 2+2 photochemical cycloaddition may be achieved by either direct photoexcitation or photosensitization. Efficient intermolecular cycloadditions are usually photosensitized. Cyclic unsaturated molecules probably have longer lifetimes than acyclic molecules, which may explain why they are effective reagents in photocycloadditions (*37*). For example, cyclopentenones (Eq. 31) and other α,β-unsaturated enones undergo a synthetically useful 2+2 cyclobutane-forming reaction (*37*). Some important applications (*38–44*) of these reactions are listed in Eqs. 32–38.



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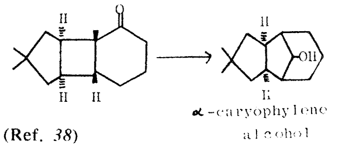

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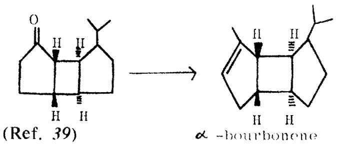
(Ref. *38*)



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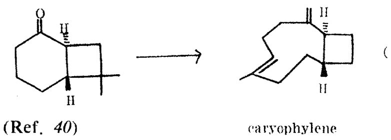

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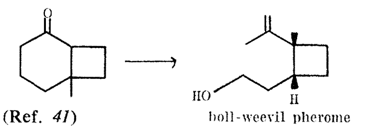
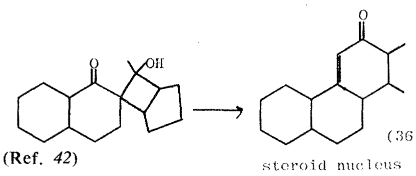


(35)

(Ref. *41*)



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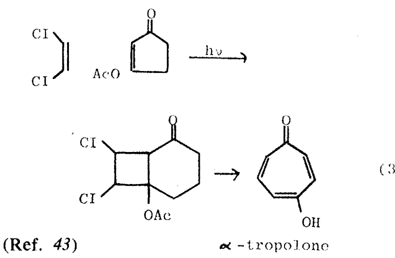
(Ref. *42*)



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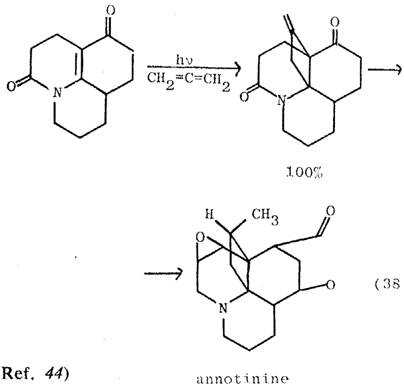
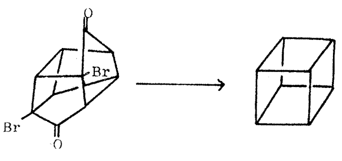


(38)

(Ref. *44*)

Intramolecular 2+2 photocycloadditions are usually reliable if the olefinic bonds can close without producing an exorbitant amount of strain. A particularly intriguing example of this reaction was employed in the first synthesis (*45*) of an all carbon "cube" structure (Eq. 39). A key in the synthesis (*46*) of β-*trans*-bergamotene **18** is a photosensitized intramolecular 2+2 cycloaddition to yield **17**.



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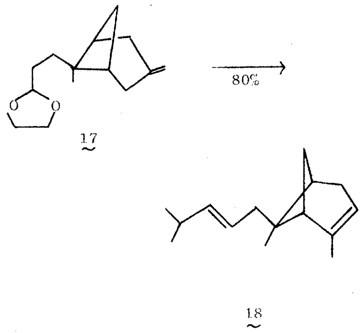
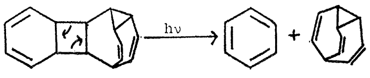


(40)

The reverse of the 2+2 reaction, that is, 2+2 photocycloeliminations, has proved to be a useful method for the preparation (*47–49*) of a number of theoretically important molecules such as bullvalene (Eq. 41), pentalene (Eq. 42), and cyclobutadiene (Eq. 43). In the latter two cases the ability to initiate the cycloelimination photochemically at low temperatures and in a solid matrix is crucial, since both pentalene and cyclobutadiene are exceedingly reactive toward self-dimerization.



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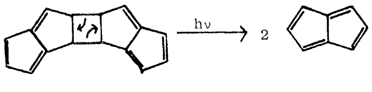

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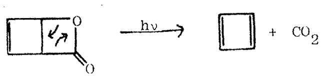
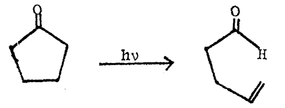


(43)

Some further extensions of classifications. Now that we have considered the reaction types that are commonly encountered in organic photoreactions, we shall discuss briefly some further applications of these reactions (i) in important general problems in synthesis, such as the design and use of photosensitive protecting and activating groups, (ii) in situations where differential excitation can lead to different photoreactions from one substrate as the result of selective direct or photosensitized excitation, and (iii) in the synthesis of a fascinating family of theoretically intriguing but difficultly accessible molecules, the $(CH)_n$ annulenes.

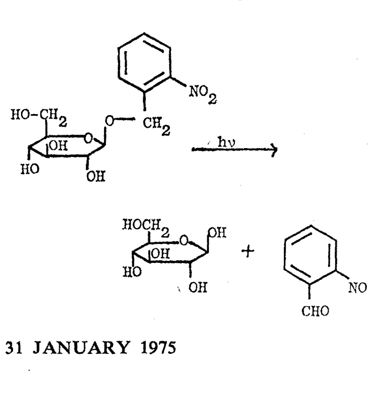
Photosensitive protecting and activating groups. An interesting idea of great potential for synthesis, but at present underexploited, is the notion of a photosensitive protecting or activating group (*50*). The general idea is to protect a functional group or activate a specific reaction path by use of a chromophore which is thermally stable, but which can be removed readily by irradiation. Fragmentation reactions in general are candidates for use as photosensitive protecting or activating groups.

For example, any photoreaction that yields an olefinic double bond is potentially useful in this regard. Thus, the type 2 cleavage (Eq. 22) and retrocycloaddition reactions of cyclobutanones (Eq. 5) and other cyclic systems (in addition to being olefin syntheses in their own right) can serve to mask a double bond. The conversion of cyclopentanones into γ,δ-unsaturated aldehydes (*51*) makes the former molecules "protecting" or "activating" groups for enals (Eq. 44).



(44)

Aromatic nitro compounds containing benzylic hydrogens in the ortho position are light sensitive and are, therefore, potential light-sensitive protecting groups for amino, carbonyl, and sulfhydryl functions in amino acids and proteins. An interesting example of the utility of this type of reaction, which possesses a further novel feature of being amenable to adaption to a light-sensitive solid polymer support (Eq. 45), is found in the protection of a hydroxyl group in D-glucose. Thus, the irradiation of 2-nitrobenzylglycosides can be used to generate the parent reducing sugars in good yield (*52*) under conditions that do not affect *o*-benzyl groups.



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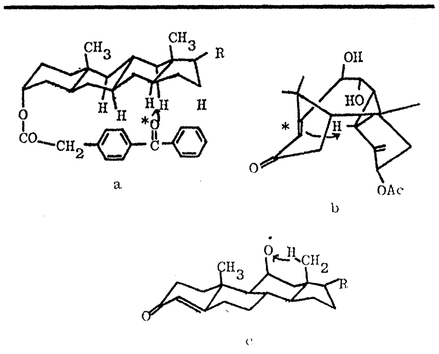
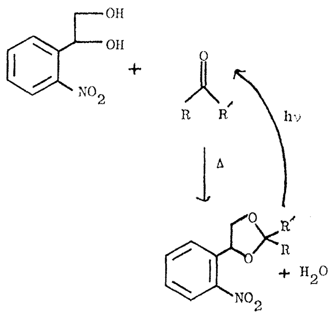


Scheme 2

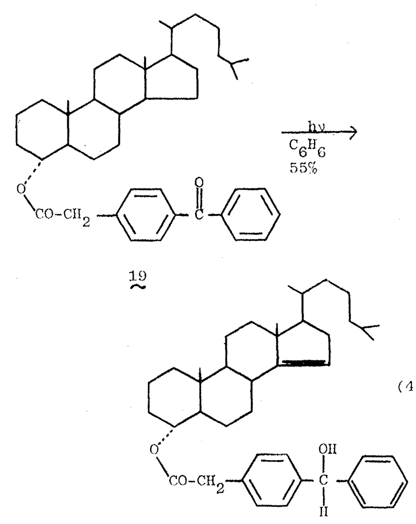
The same kind of reaction (Eq. 46) has been employed (*53*) as a photosensitive protecting group for aldehydes and ketones.



(46)

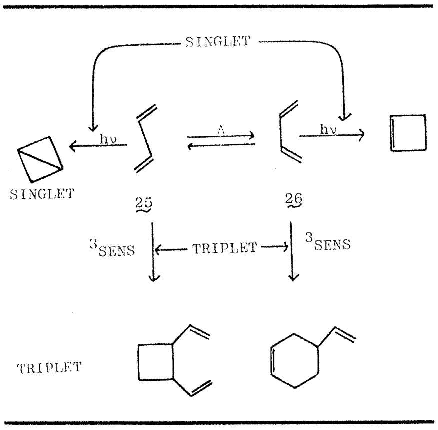
Photochemical functionalization of remote carbon atoms. For many years chemists have marveled at the occurrence of many natural processes that proceed with high reaction speed and high selectivity. A novel branch of chemistry called "biomimetic" chemistry (*54*) attempts to imitate natural chemistry in a manner that will result in useful new ideas for organic synthetic processes. For example, a commonly observed enzymatic process is one in which functionality is selectively endowed to one or two carbon atoms from a large number of apparently "synthetically equivalent" (that is, unactivated) carbon atoms. A particular case is found in steroid metabolism in which selective activation of carbon atoms is quite frequently observed. However, comparably selective synthetic methods are unavailable to the practicing organic chemist. Present theories of the high selectivity of such natural metabolic processes usually invoke special proximity effects of the reagents undergoing reaction. The reaction partners are held in an appropriate configuration for selective reaction in, say, an enzyme-substrate complex.

The latter ideas have been elegantly transposed into the realm of useful organic synthetic procedures. A particularly striking example (*54*) of a spectacular, successful system employing biomimetic chemistry is given in the photochemistry of the steroid derivative benzophenone acetic acid ester of cholestan-3-ol (**19**). Upon irradiation, this molecule (Eq. 47) undergoes a selective internal photoreduction-photoxidation that results in the highly selective introduction of a carbon-carbon double bond between C-14 and C-15.



(47)

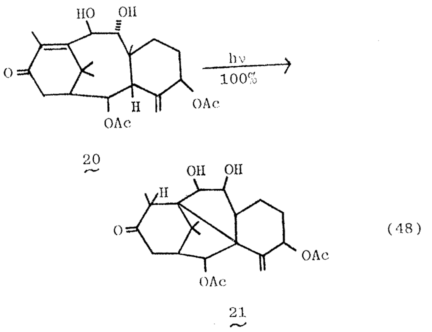
The high selectivity of the reaction is due to the fact that the carbonyl oxygen of the benzophenone must reach and abstract a hydrogen atom to initiate the reaction. Inspection of molecular models (scheme 2a) suggest that hydrogen atoms on the bottom or side of the steroid are considerably less hindered than the top or side that has the angular methyl groups serving as a barrier to close approach to the hydrogen atoms by an attacking reagent. Thus, attachment of the benzophenone reagent to an α-hydroxy group at C-3 assures that attack by photoexcited benzophenone reagent can only occur from the underside of **19**. Furthermore, models indicate that although seven axial hydrogen atoms of **19** are potentially available for abstraction, only the hydrogen atom at C-14 is optimally situated for abstraction. After abstraction of the C-14 hydrogen atom, two major possibilities exist for the ketyl-carbon radical pair which is produced: (i) coupling to form a carbon-carbon bond or (ii) transfer to form a double bond between C-14 and C-15



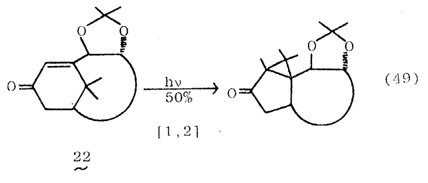
Scheme 3

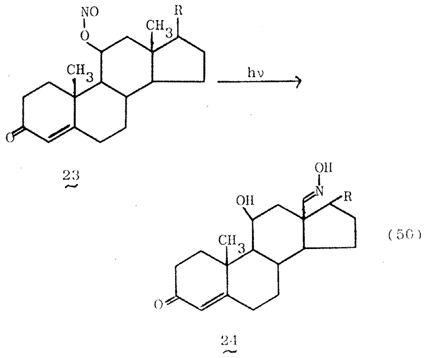
and an alcohol from the benzophenone reagent. Only the latter occurs for **19**, presumably because collapse for the carbon-carbon bond would result in a relatively strained system. The latter path is known to occur, however, in other systems for which the energetic barrier to closure is more facile. A key point in the synthesis is the apparent location of the benzophenone reagent relative to the abstractable hydrogen.

Another interesting example (*55*) of this proximity effect is given by the photoisomerization of taxinine **20** into the isomer **21** (Eq. 48). In this case a remote hydrogen is abstracted by the α-carbon of the π,π^* (triplet) state of the enone chromophore. The carbon radicals formed by this abstraction can couple because of a favorable geometry (scheme 2b) which brings them close together. The proximity requirement is again demonstrated in the photochemistry of the closely related ketal **22**, in which the α-carbon and the abstractable hydrogen are "pushed apart" because of the conformational reorganization which is forced upon the molecule by ketal formation. Photoexcitation of **22** does not lead to internal hydrogen abstraction (*55*) but instead to another reaction of cyclohexenones: a [1,2] sigmatropic rearrangement to **23**. The efficient photopathway available to **20** having been removed, **22** seeks the "next best" reaction pathway, one with well-established precedent (*35*).



A spectacular application of a proximity effect was achieved in a three-step synthesis of aldosterone (*56*) in which the irradiation of nitrite **23** causes functionalization of the C-18 methyl group of oxime **24** (Eq. 50).

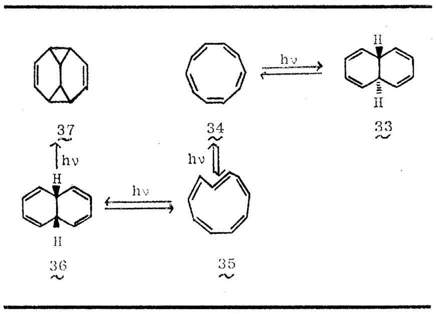




Here the photochemistry is quite ordinary: homolytic cleavage of a nitrite bond, followed by alkoxy radical hydrogen abstraction from C-18 (scheme 2c). However, the selective activation of the nitrite group under very mild conditions is not possible by nonphotochemical means.

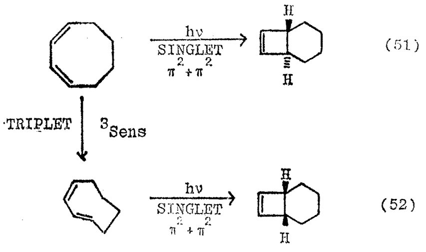
Differential singlet and triplet reactivity. Direct versus photosensitized excitation. Direct photoexcitation of an organic molecule may result in reaction from S_1 or T_1, depending on the competition between the rate of reaction of S_1 and intersystem crossing from S_1 to T_1. For molecules which do not possess an efficient $S_1 \rightarrow T_1$ conversion, photosensitization of T_1 by an electronic energy transfer mechanism is required to populate T_1. Efficient population of T_1 requires a photosensitizer which itself forms triplets efficiently and which can efficiently transfer triplet excitation. Thus, most good photosensitizers (*57*) possess a high intersystem crossing efficiency, a high triplet energy, and a relatively long triplet lifetime.

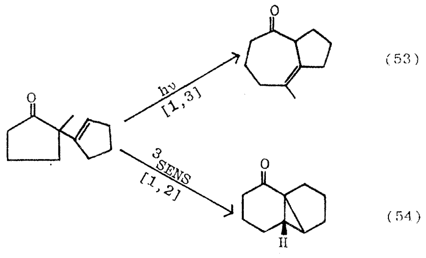
We have seen that direct photoexcitation of 1,3-dienes results in a stereospecific electrocyclic closure of the singlet state (Eq. 51). Photosensitization of 1,3-cyclooctadiene (*58*) results in *cis* → *trans* isomerization. The product may be converted by direct photoexcitation (Eq. 52) to a *trans* fused bicyclic product.



Scheme 4

As an example of the synthetic use of differential singlet-triplet reactivity is the ability to effect different photoreactions from S_1 and T_1. The direct photoexcitation (*59*) of β,γ-unsaturated enones (Eq. 53) usually results in a [1,3] sigmatropic shift (possibly a concerted singlet reaction), whereas photosensitization (Eq. 54) usually results in a [1,2] sigmatropic shift (probably a triplet reaction).



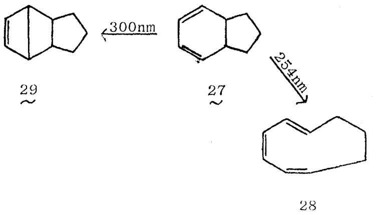


Conformational effects in organic photoreactions. According to the Franck-Condon principle, the excitation of an electron from one orbital to another occurs much more rapidly than changes in nuclear geometry. Thus, different conformers, upon direct or photosensitized excitation, produce different electronically excited molecules. These isomeric excited states may no longer be conformers in the sense that they react or decay faster than conformational equilibration. When the latter situation obtains, conformational effects on photoreactions become apparent.

A particularly informative case is found in the direct (*60*) and photosensitized (*61*) photoexcitation of 1,3-

butadiene. The latter molecule (scheme 3) is shown to exist as a rapidly equilibrating mixture of single bond *trans* and single bond *cis* conformers with the former predominating strongly. Direct excitation of the *cis* conformer probably results in electrocyclic ring closure to cyclobutene, whereas the photoexcited *trans* isomer probably is the precursor of bicyclobutane. Upon photosensitization, the two conformers are converted into *cis* and *trans* triplets which are not conformers because of the increased bonding between C-2 and C-3, which restricts interconversion and effectively renders the two triplets as configurational isomers with respect to their chemical properties. In effect, the *trans* triplet reacts with ground state butadiene to form 1,2-divinylcyclobutanes (formation of a cyclohexene from the *trans* triplet would require formation of a *trans* double bond in the cyclohexene!), whereas the *cis* triplet reacts with ground state butadiene to yield mainly vinylcyclohexene. Interestingly, photosensitizers are known which are capable of selectively photoexciting the *cis*-butadiene, and thereby resulting in high yields of vinylcyclohexene products (*62*).

Another striking example of the effect of conformation on photoreactions, which can be useful in photosynthesis of organic molecules, is the effect of wavelength on photoproducts formed from conjugated polyenes (Eq. 55). Irradiation (*63*) at 254 nm of the 1,3-cyclohexadiene **27** results in an electrocyclic ring opening to the triene **28**, whereas excitation of **27** with light of wavelength greater than 300 nm results in electrocyclic ring closure to **29**. These contrasting results are interpreted as being due to direct photoexcitation of different conformers with the different energy quanta, that is, longer wavelength light specifically excites molecules whose conformations are well suited to 1,4-closure and shorter wavelength light excites molecules that have the terminal ends of the triene chromophore in close proximity. Incidentally, since the cyclobutene absorbs at shorter wavelength than either the triene **28** or the diene **29**, use of light greater than 300 nm will result in complete conversion to **29**.

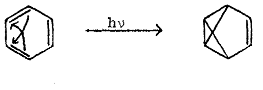


29 27 28 (55)

Photochemical syntheses of $(CH)_n$ *annulenes.* Photochemical reactions have played a crucial role in the development of the "even" annulenes, a family of hydrocarbons which have the general formula $(CH)_n$ for which n is an even number equal to or greater than 4, that is, cyclobutadiene, benzene, cyclooctatetraene, and the higher annulenes. Both photosyntheses and photoreactions of this set of hydrocarbons have provided a wealth of interesting chemistry (*64, 65*).

Cyclobutadiene, the [4] annulene, has been synthesized (*49, 66*) by several different photofragmentations (Eq. 43). Substituted cyclobutadienes have also been prepared by analogous reactions. These reactions can be run at extremely low temperatures or in rigid media. Such unusual conditions are required for the trapping of cyclobutadienes, which, as was mentioned earlier, have an enormous reactivity toward self-dimerizations. The photochemical preparation of cyclobutadienes at low temperatures and in solid matrices allows detailed study of their spectroscopic properties.

The valence isomers of benzene, that is, benzvalene (Eq. 56), Dewar benzene, and prismane (Eq. 17) were all first prepared via synthesis in which a photoreaction was used as the exclusive or as the key step in the synthesis (*67–69*). For example, benzvalene (*69*) may be prepared by direct irradiation of benzene via a photoelectrocyclic isomerization of the butadiene-bicyclobutane type. Dewar benzene may be prepared (*67*) via a photoelectrocyclic butadiene-cyclobutene rearrangement of **30** followed by an electrochemical bisdecarboxylation (Eq. 57). Prismane has been prepared via the photofragmentation of the polycyclic azo compound **10** (Eq. 17). Many other examples of photochemical preparations of valence isomers of aromatic molecules have been described (*65*).



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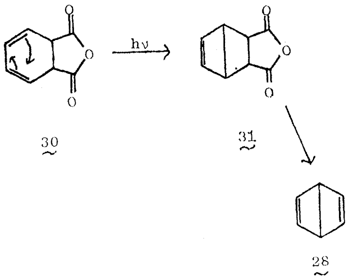
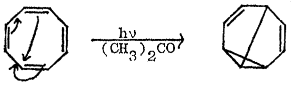


30 31 28 (57)

Cyclooctatetraene, the eight-carbon annulene, is a stable molecule, in contrast to the higher annulenes. Upon photosensitized excitation, cyclooctatetraene undergoes a photoelectrocyclic reaction of the hexatriene-bicyclo-[2.1.0]pentene variety to yield (*69*) the remarkable molecule semibullvalene (**32**). This material undergoes a series of rapid and unrelenting thermal [1,3] sigmatropic shifts which equilibrate all of the carbon atoms in the molecule.

During the last decade, many photoreactions involving ten-carbon annulenes have been described. Both all *cis*- and mono-*trans*- [ten carbon] annulenes (**34** and **35**, respectively) are involved in a rather intriguing interconnected set (scheme 4) of photoisomerizations (*64*). Thus, photoelectrocyclic ring opening of the decatetraene **33** yields **34** (conrotatory ring opening). The latter annulene can be photoisomerized to the mono-*trans* isomer **35** which, in turn, is reversibly photointerconvertible with the decatetraene **36**. At very low temperatures the latter undergoes internal photocycloaddition to the interesting structure **37**.

Several photoelectrocyclic reactions have also served as methods of preparing 12-carbon annulene (*70*) (Eq. 58).



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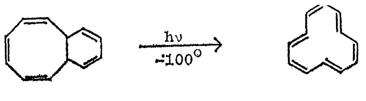

(59)

38 39

Conclusion. This article represents only a brief glimpse into one of the fascinating aspects of the chemistry of electronically excited molecules. More exhaustive coverage of synthetic applications of photochemical reactions may be found in texts and reviews. We summarize here by noting that classification of reliable photoreactions is possible, but that the most effective application of the classification scheme requires a familiarity with some of the special features of the chemistry of electronically excited states. Thus, knowledge of the properties of singlet and triplet states, the factors which determine photochemical efficiency and reactivity, and the special technical aspects of photochemical procedures such as selective direct and photosensitized excitation and photoexcitation at low temperatures or solid matrices make photochemistry a useful tool for the construction of organic molecules. It is our hope that the material and flavor of this article will whet the intellectual and experimental appetites of researchers who are concerned with various aspects of the synthesis of organic molecules.

References and Notes

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