Predicting Selectivity in Thermal Cycloaddition Reactions

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In thermal cycloaddition reactions of large molecules where many products are allowed by orbital symmetry, the preferred reaction paths can be predicted by considering the formation and closure of a *hypothetical* intermediate diradical. The diradical should be formed by addition at the end of each conjugated polyene chain, and the preferred closures take place at the ends of the conjugated radicals thus produced. If all thermal cycloaddition reactions thus produced are not allowed by orbital symmetry, end-to-middle closures are next most favorable.

Until the advent of the Woodward–Hoffmann rules,[1] cycloaddition reactions of the larger conjugated polyenes were rarely explored, because of the large number of possible products that were expected from such reactions. The application of orbital symmetry principles to cycloaddition reactions simplified the problem by showing that the occurrence of many reactions that had earlier been thought possible was forbidden by the nature of the electronic structures of the molecules. There is still a problem remaining, however, since in large molecules there can be many allowed cycloadditions, and orbital symmetry arguments cannot help to predict which of the allowed reactions should be favored; many recent experiments have shown such reactions to be extremely selective.[2-10]

Several methods for calculation of reaction paths have been proposed,[11-13] that are in principle applicable to the present problem; such methods are either too complex for routine use by the chemist interested in synthesis, or not sufficiently reliable for such use.[14]

I report here a simple scheme that is in excellent agreement with reported experimental results, and can be used in conjunction with the Woodward–Hoffmann rules to make predictions for thermal cycloadditions.
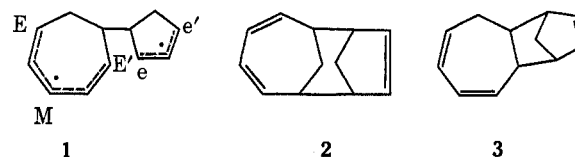
The starting point for the scheme is the well-known formalism of approximating the Diels–Alder reaction as a two-step reaction with a diradical intermediate, which correctly predicts the products of reactions of unsymmetrically substituted dienes and dienophiles.[15] Applying the formalism of a hypothetical diradical intermediate to a thermal cycloaddition reaction between two larger conjugated polyenes leads, after consideration of the stabilities and reactivities of the hypothetical intermediate diradicals, to the following rules for predicting (I) the formation and (II) the closure of a diradical.

(I) In diradical formation, the most conjugated radical is formed by addition to a terminus of a polyene chain; so a diradical should be formed by *end-to-end addition*.

(II) In diradical closure, (A) each polyene radical thus formed reacts at its terminus to give *end-to-end closure*, if the overall cycloaddition is allowed by orbital symmetry; (B) if the cycloaddition arising from closure IIa is orbital-symmetry forbidden, *end-to-middle closure* is next most favored.

An example of applying this scheme would be instructive. For the thermal reaction of cycloheptatriene with cyclopentadiene, five reactions are allowed by orbital symmetry. Application of rule I gives di-

radical **1** to be considered. Closures E–e and E'–e are forbidden (for all-syn cycloadditions), since they are $_\pi6 + _\pi2$ and $_\pi2 + _\pi2$ cycloadditions, respectively. Closure M–e, although symmetry allowed, is predicted by the scheme to be disfavored since allowed end-to-end reactions are possible here. Closures E–e' and E'–e' give $_\pi6 + _\pi4$ adduct **2** and $_\pi4 + _\pi2$ adduct **3**, respectively, as the products predicted by the proposed method.[16] Although this reaction has not been reported, three very similar reactions have appeared in the recent literature: (A) reaction of a substituted cyclopentadienone with cycloheptatriene gives products of types **2** and **3**;[7] (B) reaction of tropone with cyclopentadiene gives a product of type **2**;[4] (C) reaction of tropone with a substituted cyclopentadienone gives a product of type **2**,[8] accompanied by a small quantity of an adduct whose formation is most easily rationalized by a dipolar mechanism.

(1) R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969), and references cited therein.

(2) W. v. E. Doering and D. W. Wiley, *Tetrahedron*, **11**, 183 (1960).

(3) E. LeGoff, *J. Amer. Chem. Soc.*, **84**, 3975 (1962).

(4) R. C. Cookson, B. V. Drake, J. Hudec, and A. Morrison, *Chem. Commun.*, 15 (1966).

(5) G. Schröder and W. Martin, *Angew. Chem., Int. Ed. Engl.*, **5**, 130 (1966).

(6) S. Itô, Y. Fujise, and M. C. Woods, *Tetrahedron Lett.*, 1059 (1967).

(7) K. N. Houk and R. B. Woodward, *J. Amer. Chem. Soc.*, **92**, 4143 (1970).

(8) K. N. Houk and R. B. Woodward, *ibid.*, **92**, 4145 (1970).

(9) K. N. Houk, L. J. Luskus, and M. S. Bhacca, *ibid.*, **92**, 6392 (1970).

(10) G. C. Farrant and R. Feldmann, *Tetrahedron Lett.*, 4979 (1970).

(11) K. Fukui, *Accounts Chem. Res.*, **4**, 57 (1971), and references cited therein.

(12) (a) L. Salem, *J. Amer. Chem. Soc.*, **90**, 543, 553 (1968); (b) A. Devaquet and L. Salem, *ibid.*, **91**, 3793 (1969); (c) A. Devaquet, *Mol. Phys.*, **18**, 233 (1970).

(13) R. Sustmann and G. Binsch, *ibid.*, **20**, 1, 9 (1971).

(14) Calculations were performed according to the methods of Fukui (ref 11) and Salem (ref 12a) for all the reactions considered in the present work; the products which have been observed were only rarely predicted by the calculations.

(15) Y. A. Titov, *Russ. Chem. Rev.*, **31**, 267 (1962), and references cited therein. For discussion of the important question of the degree of concert in the Diels–Alder reaction, see M. Taagepera and E. R. Thornton, *J. Amer. Chem. Soc.*, **94**, 1168 (1972), and references cited therein, and W. v. E. Doering in "XXIIIrd International Congress of Pure and Applied Chemistry," Vol. 1, Butterworths, London, 1971, pp 237–250.

(16) The stereochemistry of these reactions has been predicted to be endo for the $_\pi4 + _\pi2$ and exo for the $_\pi6 + _\pi4$ reactions (ref 1, 17); the latter prediction has been experimentally confirmed in all known cases, and the former generalization is the well-known Alder endo rule. Houk (ref 18) has carried the prediction further, to generalize that $[_\pi4_m + _\pi2]$ cycloadditions should be endo when extending conjugation is present in the 2-π system, and $[(_\pi4_m) + (_\pi4_n + _\pi2)]$ ($n \neq 0$) reactions should be exo.

(17) R. Hoffmann and R. B. Woodward, *J. Amer. Chem. Soc.*, **87**, 4388 (1965).

(18) K. N. Houk, *Tetrahedron Lett.*, 2621 (1970).

TABLE I
EVALUATION OF PREDICTION METHOD

Compounds	No. of allowed products[a]	No. found	No. predicted[b]	No. found bad fit to I	No. found bad fit to IIa	No. found bad fit to IIb[c]	No. found not predicted	No. predicted not found	Ref
Cyclo-C_7H_8 + cyclopenta-dienone (substituted)	5	2	2	0	0	0	0	0	7
Tropone + cyclo-C_5H_6	5	1	2	0	0		0	1	4
Tropone + cyclopentadien-one (substituted)	5	2[d]	2	0	0		1[d]	1	8
Tropone + cyclo-C_7H_8	8	1	4	0	e	0	0	3	6
Tropone + dimethylfulvene[f,g]	9	2	4	0	e	0	0	2	9
Cyclooctatetraene dimer[g]	4	1	1	0	0		0	0	5
Heptafulvene + dimethyl acetylenedicarboxylate (DMA)	2	1	1	0	0		0	0	2
Ph_6-Pentalene + DMA	3	1	1	0	0		0	0	3
1,6-Dimethylene-2,4-cyclo-heptadiene + TCNE	2	1	1	0	0		0	0	10
Totals	43	12	18	0	0	0	1	7	

a Without considering stereochemistry (exo or endo), valence tautomers, or reaction products that violate Bredt's rule. *b* By I and IIa, or I and IIb if necessary. *c* If IIa is not allowed. *d* Including adduct through carbonyl group (see text). *e* Closure according to IIa forbidden. *f* Only 1:1 adducts considered. *g* Only initial products considered.

These results, together with the results of similar treatments of some other reported cycloaddition reactions, are collected in Table I, which clearly shows that this scheme is in good accord with the experimental facts. It will be noted that the proposed scheme occasionally predicts too many products for a reaction, but, except in the one case where there is a competing polar reaction, the prediction always includes all the known products.

The assumption that a concerted cycloaddition reaction may be approximated by a two-step reaction with a diradical intermediate may be justified by the empirical successes of the proposed scheme[19] and of the diradical method for predicting Diels–Alder reactions. Beginning with this approximation, the success of the two end-to-end rules is not surprising, since all reactivity indices calculated for alternant hydrocarbon polyenes, including free valence and electron density in the highest occupied molecular orbital (for even alternant hydrocarbons) and self-polarizability (for even alternant hydrocarbons and odd alternant radicals), predict this kind of terminal reactivity. Such reactivity indices correctly predict, for instance, the observed coupling of radical **4** (a presumed intermediate

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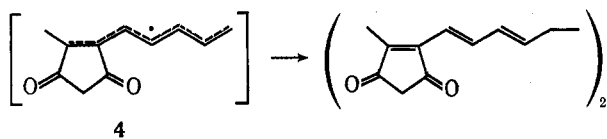
in the oxidation of pyrethrolone[20]). However, it is worthy of note that, in cases other than the open-chain alternant polyenes, use of such calculated parameters is *less* uniformly successful in predicting cycloaddition

products than is the present set of qualitative rules (including the formalisms described below). Neither polarizabilities, localization energies, nor perturbation methods are consistently helpful when the qualitative scheme predicts too many products.

The cross-conjugated starting materials deserve additional comment. In reactions of cyclopentadienone or tropone, we should predict that addition will occur at the 2 position to give radical **5**, since the carbonyl

5
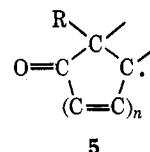
group does not stabilize a radical center on the adjacent carbon more than does a methylene group.[21] Thus the carbonyl group has little effect on the reaction path, and cycloadditions of cyclopentadienone resemble those of cyclopentadiene, reactions of tropone resemble those of cycloheptatriene (except for norcaradiene reactions), etc. In the analogous cases of fulvene and related compounds, not enough experimental data are available to justify a choice between a linearly conjugated cyclic radical such as **6** and the cyclic conjugated radical **7**.

6   **7**
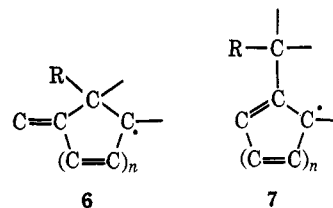
The choice that the formation of **6** is preferable to that of **7** gives predictions that are consistent with the observed cycloadditions of fulvene[9] and heptafulvene;[2] this preference is consistent with the Hückel self-polarizabilities calculated for the starting materials, but *not* with the Hückel energies of the radicals.

It is apparent from the success of the method that

(19) The success of the diradical intermediate in predicting reactions may or may not be entirely relevant to the mechanisms of these reactions, since even a very small lack of synchronism in bond formation, associated with a small amount of diradical character in the transition state, may be product-determining. It should also be pointed out that, even in the cases where there is a symmetry plane relating the new bonds in the product, a plane of symmetry is not rigorously required in the transition state leading to that product [*cf.* Salem's discussion of "through the mirror" and "around the mirror" paths for narcissistic reactions: *Accounts Chem. Res.*, **4**, 322 (1971)].

(20) L. Crombie, J. A. Ellis, R. Gould, G. Pattenden, M. Elliot, N. F. Janes, and K. A. Keffs, *J Chem. Soc. C*, 9 (1971).

(21) K. D. King, D. M. Golden, and S. W. Benson, *J. Amer. Chem. Soc.*, **92**, 5541 (1970), and references cited therein.

alkyl and aryl substituents can be ignored, as a first approximation, although, in those cases where there is a selectivity among reactions predicted by the proposed method, that selectivity may arise in part from a combination of the effects of substituents on polarity, polarizability, and steric bulk. The effect of heteroatomic substituents (other than carbonyl) is not easily rationalized in the framework of the present scheme.[22]

Two problems remain; the first has to do with valence tautomerism in the starting materials. For instance, no way has been found within the present scheme to aid in explaining the difference between cyclooctatetraene reacting with itself ($_\pi 8 + _\pi 2$) in monocyclic form,[5] and reacting with most dienophiles ($_\pi 4 + _\pi 2$) as the bicyclic valence tautomer.[23]
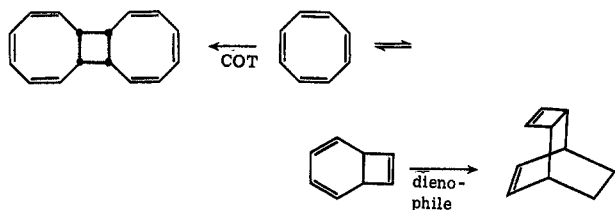
The second problem is concerned with stereochemistry. Particularly in borderline cases, it is difficult to assess how much effect the spatial arrangements of the atoms will have on the course of a cycloaddition reaction. The reactants in Table I are for the most part geometrically constrained in such a way that the distinctions between stereochemically plausible and im-

(22) Note, for instance, the differences between tropone and 2-chlorotropone on reaction with cyclopentadiene [S. Itô, K. Sakan, and Y. Fujise, *Tetrahedron Lett.*, 775 (1969)].

(23) G. Schröder, "Cyclooctatetraen," Verlag Chemie, Weinheim, 1965, pp 48–50.

plausible reactions are relatively clear-cut; for instance, anti cycloadditions are unlikely in all these cases. Exceptions to this situation are likely to occur.

Applications of the proposed method to predict the products from several simplified model systems are shown in Table II. Neither the steric likelihood of each

TABLE II
PREDICTIONS FOR MODEL COMPOUNDS[a]

[a] Only all-syn additions of open-chain valence tautomers are considered. No stereochemistry about double bonds is intended by the structural formulas.

reaction nor the possibility of valence tautomerism has been considered in making the predictions in this table.

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Carbenoids with Neighboring Heteroatoms. III. Electrophilic Reactions of Two α-Halocyclopropyllithium Compounds[1a,b]

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Solutions of carbenoids 4a and 11a were prepared by the reaction of alkyllithiums with dihalocyclopropanes 1. Carbenoid 4a had limited stability at −80° but could be trapped by carbonation which gave 2 in low yield and by protonation which gave 4b in high yield. Bicyclobutane 5 was the major product of thermal decomposition of 4a. Carbenoid 11a was more stable at −80° as evidenced by reactions with H_2O, D_2O, and benzophenone. Thermal decomposition of 11a at −20° gave diene 14, presumably *via* dimerization of 1-methoxycyclohepta-1,2-diene (16).

We recently reported on the stereoselective preparation and nucleophilic reactivity of intramolecularly stabilized α-halocyclopropyllithium reagents.[1b] With the aim of preparing stereochemically known α-halolithium reagents which display the entire range of carbenoid reactivity, we have been investigating the structural requirements for the preparation of stabilized carbenoids. In this paper we wish to report on some nucleophilic and two electrophilic reactions (C–H

insertion, allene formation) of the carbenoids derived from 1-methoxy-7,7-dihalobicyclo[4.1.0]heptane (1).

The Carbenoid from 1-Methoxy-7,7-dichlorobicyclo[4.1.0]heptane.—Treatment of the known[2] dichloronorcarane derivative 1a with 1 equiv of ethereal butyllithium for 10 min at −80° followed by carbonation of the reaction mixture afforded a 7% yield of a neutral, crystalline product formulated as 2. The structure of 2 rests on the following data and reasoning. We had previously encountered an α-chloro-γ-lactone, 3, from the carbonation of 7-*exo*-chloro-2-oxabicyclo-

(1) (a) Supported in part by Grant 970-G1 from the Petroleum Research Fund, administered by the American Chemical Society, and in part by Grant GP-9543 from the National Science Foundation. (b) Part II: K. G. Taylor, W. E. Hobbs, and M. Saquet, *J. Org. Chem.*, **36**, 369 (1971). (c) NASA Trainee, 1966–1968.

(2) D. G. Lindsay and C. B. Reese, *Tetrahedron*, **21**, 1673 (1965).