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Mechanistic Aspects of Photocycloaddition Chemistry. An Interesting Relationship between Substituent Effects on 1,4-Biradical Closure-to-Cleavage Ratios and Photocycloaddition Regioselectivity

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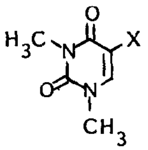
Summary. *The influence of β-substituents on closure-to-cleavage ratios of triplet 1,4-biradicals has been recorded and compared with how these substituents influence the regiochemistry of photocycloaddition of isobutylene and 5-substituted uracils.*

A knowledge of the factors which influence the regiochemistry of photochemical cycloaddition reactions of α,β-unsaturated carbonyl systems is of mechanistic and synthetic interest.[1,2] We report herein a study which delineates the role of substituents in altering the regiochemistry of 5-substituted uracil photocycloadditions to isobutylene.[3] The results are of general interest in photochemical cycloaddition and 1,4-biradical chemistry.

The regiochemical outcome of the photocycloaddition of 5-substituted uracils to isobutylene is dramatically dependent on the 5-substituent, as shown in the table.' The 5-trifluoromethyl, 5-acetyl ketal, 5-trimethylsilyl, and 5-fluoro groups on the uracil give nearly exclusively the head-to-tail adducts 2 (entries 5-8), while the 5-methoxyuracil affords nearly exclusively the head-to-head adduct 3 (entry 9), and the remaining substituents give a mixture of regioisomers (entries 1-4). While the synthetic ramifications of these results were of interest, we are most concerned with the origin of this substituent effect on regioselectivity. According to the generally accepted mechanism of photochemical cycloaddition (scheme),[4] the regiochemical outcome could be influenced at two stages of the reaction. First, a specific orientation in the exciplex would translate into a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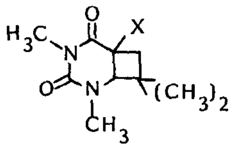
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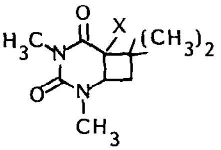
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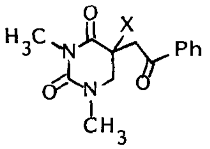
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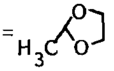
a, X = CN; b, X = CH_3; c, X = H; d, X = CO_2CH_3; e, X = CF_3; f, X = 
g, X = $Si(CH_3)_3$; h, X = F; i, X = OCH_3

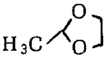
Scheme

Abbreviated Mechanism for Photocycloaddition of Triplet Enone and Olefin

Enone^{*3} + Olefin ⟶ [Exciplex]^{*3}
[Exciplex]^{*3} ⟶ [1,4-Biradical]^{3}
[1,4-Biradical]^{3} ⟶ Products
[1,4-Biradical]^{3} ⟶ Enone + Olefin

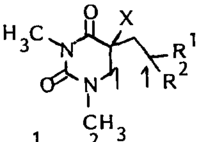
regiochemical preference in the product. This idea, first suggested by Corey,[5] has been explored theoretically.[4c,6] Second, if isomeric biradicals such as 5 and 6 are intermediates in the reaction, then factors which affect the closure-to-cleavage ratios of these biradicals would also influence the regiochemistry of the product.[1b] While the importance of exciplex orientation is a difficult, if not impossible, question to answer, the second possibility can be explored experimentally. Our approach[3d] was to generate model 1,4-biradicals which would be substituted with the same groups as are present in the uracils of the table. If no correlation is noted between biradical closure-to-cleavage ratios and the regiochemistry of the photocycloaddition, then either 1,4-biradicals are not intermediates in the photocycloaddition reaction or other factors are largely responsible for the regiochemistry of the photocycloadditions.

Table. Photochemical Results from 1[a,b] and 4[b,c]

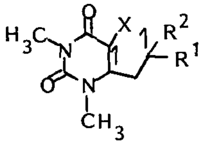
entry	X	ratio 2:3 from 1	ratio cyclobutanols/ acetophenone from 4
1	a, CN	1:1	0.33:1
2	b, CH_3	1.5:1	0.42:1
3	c, H	2.0:1	0.25:1
4	d, CO_2CH_3	4:1[d]	0.63:1
5	e, CF_3	32:1[d]	2.1:1
6	f, 	>50:1[d,e]	4.9:1
7	g, $Si(CH_3)_3$	>50:1[e]	3.1:1
8	h, F	>50:1[e]	>10:1[f]
9	i, OCH_3	0.04:1	0.60:1

[a] Isolated yields of 2 and 3 ranged from 63 to 100%. [b] All products showed spectroscopic and analytical data in agreement with the assigned structures. [c] Ratios reported by integration of 200-MHz ^{1}H NMR spectrum were in qualitative agreement with those determined by isolation. [d] In the case of 1d-f cycloadditions, ene products corresponding to the regiochemistry of 2 were isolated in yields of 20, 6, and 4%, respectively. [e] Regioisomers corresponding to 3 not detected. [f] Acetophenone was detected by GLC but was not isolated. A photochemically promoted elimination of hydrogen fluoride gave 5-phenacyl-1,3-dimethyluracil in 47% yield at 0 °C.

It was critical that an unambiguous method of triplet 1,4-biradical generation be used for comparison of the triplet sensitized photocycloaddition results with the closure-to-cleavage ratio of the 1,4-biradical. Since the Type II reaction of an aromatic ketone[7] has been shown unequivocally to generate triplet 1,4-biradicals,[8,9] we have examined the chemistry of 4a-i. It was felt that the effect of substituents on the closure-to-cleavage ratios of biradical 7 could serve as a good model for the same effect on biradical 5.[10]



5, $R^1 = R^2 = CH_3$
7, $R^1 = OH$, $R^2 = Ph$



6, $R^1 = R^2 = CH_3$

Irradiation of 4c in benzene gave a 4:1 ratio of acetophenone and uracil to cyclobutanol with a quantum yield for appearance of acetophenone of 0.51 and a quantum yield for disappearance of 4c of 0.66. The quantum yields remained constant for benzene solutions containing 0-50% of *t*-butyl alcohol. Standard Stern-Volmer quenching studies using 2,5-dimethyl-2,4-hexadiene as the quencher gave $k_r = 1.4 \times 10^8$ sec^{-1} and $k_d = 1.3 \times 10^8$ sec^{-1}. Except for the appreciable value of k_d, the excited state parameters for 4c are comparable to values reported for butyrophenones.[11,12] Having established that the photochemistry of 4c was similar to that of other butyrophenones, the products from the remaining butyrophenones were studied, and the ratios of cyclobutanol(s) to acetophenone were determined (table). In every case except one (the methoxy systems 1i, 4i), the effect of the substituent on the closure-to-cleavage ratio of the biradical model, 7, correlates with the effect that the same substituent has on the regiochemistry of the photocycloaddition reaction of the respective uracil derivative (Fig. 1).

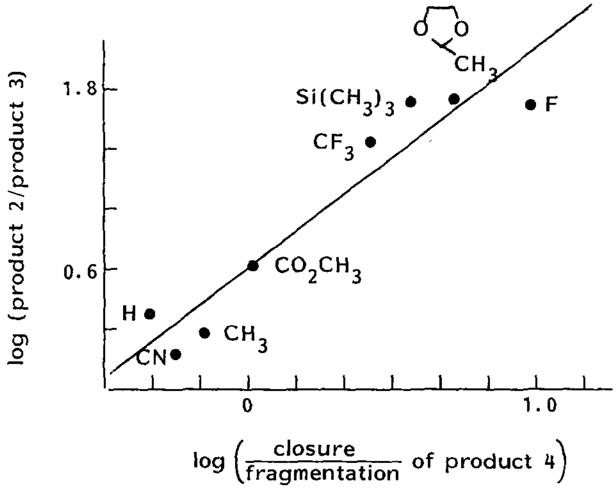


Figure 1. Correlation of substituent effect on photoaddition regiochemistry and closure-to-cleavage products from model 1,4-biradical. The line is drawn only to emphasize the relationship.

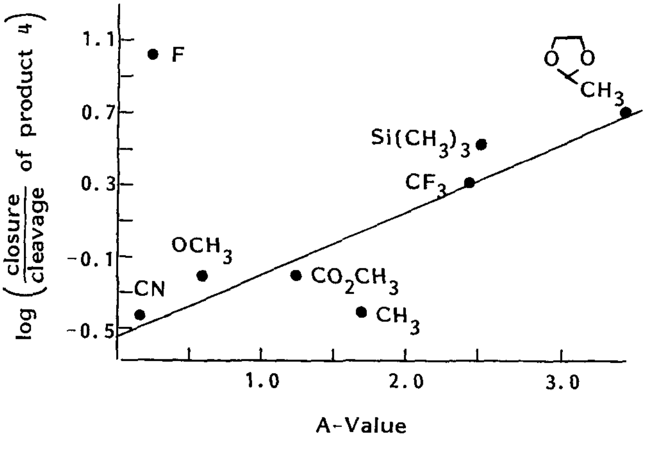


Figure 2. Correlation of closure-to-cleavage ratio of product 4 versus A-value of the substituent. The line is drawn only to emphasize the relationship.

Very little is known about the effects of β-substituents on closure-to-cleavage ratios in 1,4-biradicals. Previous studies on the Norrish Type II reaction of butyrophenones have shown that β,β-dimethyl substituents decrease the yield of cyclobutanol to 3% (butyrophenone gives 12% cyclobutanol).[13] The present study shows that replacement of the β-hydrogen in this system with other substituents leads to extremely large changes in the ratio of cyclobutanol to cleavage products. The diverse type of substituents which lead to the increased closure-to-cleavage ratios herein argues against only an electronic explanation for the results. Furthermore, a plot of A-value[14] vs. log [closure/cleavage of 4a-g,i] is reasonably linear, suggesting a steric origin for the effect, except for the case of fluorine. While the precise nature of the steric effect remains unknown, it undoubtedly concerns the different stereoelectronic requirements for closure versus cleavage of 1,4-biradicals. Apparently, large 5-substituents in these systems favor transition states for closure relative to cleavage.[7,11]

For the first time a direct correlation has been noted between the yield of a regioisomer in an enone-type photocycloaddition and an increased propensity of a model 1,4-biradical, which leads to that regioisomer, to undergo the closure reaction. Only for 5-methoxyuracil, which shows a very unusual preference for formation of the sterically hindered head-to-head product, is there no correlation. Undoubtedly another factor, perhaps exciplex orientation, plays an important role in the regiochemistry observed in this system. The results presented herein suggest that structural changes in the enone which favor closure over cleavage for a particular biradical intermediate could be employed to enhance the regiochemistry of a photocycloaddition. A second point is the exceptionally high closure-to-cleavage ratio observed with the fluoro-substituted compound, 4h. This does not correlate with the A-value for fluorine and provides yet another example of unusual chemistry associated with biradical centers containing a fluoro substituent adjacent to a radical center.[3b,3e,15] We hope to report further on the anomalous behavior of the fluoro substituent in biradical reactions in the near future.

Acknowledgment is made to the Donors of the Petroleum Research Fund administered by the American Chemical Society for support of this research.

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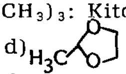
14. The A-values were obtained as follows: (a) F, CN, OCH_3, CO_2CH_3, CH_3: Eliel, E. L.; Allinger, N.L. *Topics in Stereochemistry* 1967, Vol. 1. (b) CF_3: Della, E.W. *J. Am. Chem. Soc.* **1967**, *89*, 5221. (c) $Si(CH_3)_3$: Kitching, W.; Olszowy, H.A.; Drew, G.M.; Adcock, W. *J. Org. Chem.* **1982**, *47*, 5153. (d)  : estimated value.

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