

Intersystem Crossing in Triplet 1,4-Biradicals: Conformational Memory Effects on the Stereoselectivity of Photocycloaddition Reactions¹

AXEL G. GRIESBECK,* HARALD MAUDER, AND STEFAN STADTMÜLLER

Institut für Organische Chemie, Am Hubland, D-97074 Würzburg, Germany

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Biradicals have been postulated as intermediates in many organic reactions and described in excellent articles.² Even ground-state transformations allowed from the Woodward-Hoffmann orbital symmetry rules have been discussed as proceeding via 1,*n*-biradicals.³ The latter assumptions usually originate from calculations rather than from experimental facts. In the photochemistry of triplet excited species, i.e., triplet alkenes or triplet carbonyl compounds, however, the existence of long-lived triplet 1,*n*-biradicals has been established by a multitude of experimental observations such as transient spectroscopy in solution or in matrix (ESR,⁴ UV/vis,⁵ CIDNP,⁷ photoacoustic calorimetry⁸), trapping experiments (with triplet oxygen,⁹ alkenes¹⁰), radical clocks,¹¹ or electron-transfer quenching.¹² In many cases the structure of the products and the regio- and stereoselectivity of their formation were correlated with the structure of the intermediary biradicals and with differences in radical stability.¹³

The most important difference concerning biradicals in ground-state chemistry and photochemistry is the spin-imposed barrier for triplet to singlet intersystem crossing (ISC), which leads to a dramatic increase in lifetime. Whereas singlet biradicals are separated from closed-shell products only by a small barrier (if any), triplet biradicals have to undergo a forbidden spin change process to reach a singlet energy surface. Because of the enhanced lifetimes of triplet biradicals, stereochemical information originating from the starting material can be wiped out during the phototransformation.¹⁴ In contrast to this, many photoreactions *via* singlet states are known to proceed with retention of configuration of the starting materials.¹⁵ This "memory effect" is due to the very short lifetimes of singlet transients, where rotation around single bonds cannot compete with the formation of a new bond. As a consequence of this effect a decrease in stereoselectivity should be observable in photoreactions proceeding *via* triplet biradicals.

Axel G. Griesbeck was born in 1958, studied at the University of Munich, and received his doctoral degree in chemistry with Klaus Gollnick in 1984. He did postdoctoral research with Waldemar Adam at the University of Würzburg (1985-1986) and Dieter Seebach at the ETH Zürich (1986-1987). In 1991 he finished his Habilitation at the University of Würzburg and was appointed Privat-Dozent at the Department of Organic Chemistry. He was a visiting professor at the University of Wisconsin in Madison in fall 1993. His current research interests are preparative and mechanistic organic photochemistry, the synthesis of polyquinanes, gas-phase thermolyses, and unnatural amino acids and amino acid derivatives.

Harald Mauder (born 1962) received his doctoral degree at the University of Würzburg in 1992. Currently he is a postdoctoral fellow with Meir Lahav at the Weizmann-Institute of Science in Rehovot, Israel.

Stefan Stadtmüller (born 1963) received his doctoral degree at the University of Würzburg in 1991. From 1991 to 1993 he was a postdoctoral fellow with Curt Wenstrup at the University of Queensland in Brisbane, Australia.

Lifetime of Triplet 1,*n*-Biradicals

The lifetime of triplet 1,*n*-biradicals usually is determined by the intersystem crossing rate ($\tau_{BR} = 1/k_{ISC}$). This means that the biradical has to stay in the triplet manifold for a certain time, because without spin flip it cannot undergo bond formation or bond cleavage. These steps would lead to triplet excited species and thus would be highly endergonic.¹⁶ Three mechanisms operate for the interaction between singlet and triplet states of 1,*n*-biradicals: electron-nuclear hyperfine coupling (HFC), spin-lattice relaxation (SLR), and spin-orbit coupling (SOC).¹⁷ HFC is an important control factor for biradicals with long carbon chains between the radical centers.¹⁸ SOC plays the dominant role in biradicals with shorter distances between the radical centers, whereas SLR seems to contribute only marginally.

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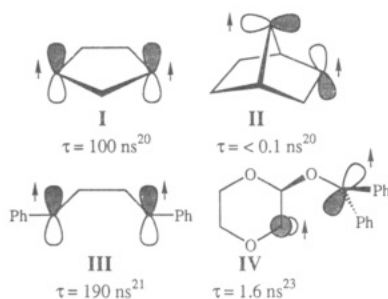
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In contrast to the other mechanisms SOC is strongly dependent on the geometry of the triplet biradical. This was first summarized in three rules stated by Salem and Rowland¹⁹ in 1972: (a) SOC decreases with increasing distance between the two spin-bearing atoms. Because there is also the possibility of through-bond interaction, not only is the actual distance between the two radical centers important (corresponding to a conformational dependence) but also the number of bonds ($n - 1$). (b) Conservation of total angular momentum could be achieved when the axes of the p orbitals at the radical centers are oriented perpendicular to each other. (c) SOC is proportional to the ionic character of the singlet state. Summarizing these three rules, a pronounced conformational and structural dependence should result for the lifetimes of triplet biradicals. A numerical equation for SOC ($\text{SOC} = B(R)|S| \sin \phi$) was given by Doubleday et al.²⁰ $B(R)$ is a function of the distance R between the radical centers, ϕ the angle between the p orbitals at these positions, and $|S|$ the overlap integral for these orbitals. A remarkable success of these rules is the explanation of 1,3-biradical lifetimes for triplet 1,3-cyclopentadienyl (I, $\tau = \text{ca. } 100 \text{ ns}$) and for bicyclo[2.2.1]heptane-2,7-diyl (II, $\tau < 100 \text{ ps}$).²¹ In the latter case the interorbital angle is about 60° , providing a favorable SOC geometry for rapid intersystem crossing. Less pronounced were the effects for 1,4-biradicals which are intermediates in such important reactions as the Paternò-Büchi and the de Mayo photocycloaddition as well as in Norrish type II processes.



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In contrast to rather long-lived tetramethylenes (e.g., biradical III with $\tau = 190 \text{ ns}$),²² the 2-oxatetramethylenes (preoxetanes) formed during the Paternò-Büchi reaction or the photolysis of α -alkoxy carbonyl compounds²³ are much shorter lived. For the triplet biradical (IV) from benzophenone and 1,4-dioxene, a lifetime of 1.6 ns was determined by laser flash photolysis.²⁴ Other Paternò-Büchi biradicals which were investigated cover a lifetime range of 1–7 ns.²⁵ SOC constants have been calculated for tetramethylene and 2-oxatetramethylene, clearly demonstrating that SOC is the important mechanism for ISC in both biradical families, with SOC values about 20 times higher for the oxygen analogue.²⁶ The lifetime of a triplet 2-oxatetramethylene, however, still is long enough to ensure rotation around the central O–C single bond. For example, benzophenone addition to *cis*- and *trans*-2-butene gives the same product ratio of diastereomeric *cis*- and *trans*-oxetanes, respectively.²⁷

We report here the investigation of a series of [2 + 2]-photocycloaddition reactions with the purpose of showing that the appropriate ISC conformation (according to the Salem–Rowland rules) is reflected in the stereoselectivity of product formation. This parameter was neglected in nearly all investigations on triplet biradical lifetimes and structure correlations which have appeared up to now. Assuming optimal geometries, on one hand, at which intersystem crossing should be preferred and very short singlet biradical lifetimes, on the other hand, should allow the prediction of the preferred configuration of the photochemically produced species. The evaluation of this concept is the subject of this Account.

Model Systems for the Paternò-Büchi Reaction

In order to investigate influences on the stereoselectivity of [2 + 2] cycloadditions between triplet carbonyl compounds and alkenes, the amount of competing reactions (hydrogen abstraction, etc.) had to be minimal. Furthermore, the regioselectivity of the Paternò-Büchi reaction²⁸ should be as high as possible and the products stable to subsequent photolysis to guarantee a small range of reaction products and simplify the analysis. It was also necessary to consider the borderline between biradical and electron-transfer mechanisms which sets a limit in the use of highly electron rich alkenes as 2π -components. We chose cyclic alkenes (in order to restrict conformational flexibility) with an oxidation potential higher than 0.7 V as model compounds and investigated the photoreaction with benzaldehyde (1a). This carbonyl addend

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Table 1. Photocycloaddition of Benzaldehyde to Cycloalkenes: *Endo/Exo* Diastereoselectivity

		<i>endo</i> : <i>exo</i>	yield oxetane [a]	ref(s)
	(2)	88 : 12	98	30
	(3)	61 : 39	55	28
	(4)	74 : 26 80 : 20	34	28
	(5)	90 : 10	45	28
	(6)	66 : 34	95	29
	(7)	52 : 48	83	29
	(8)	66 : 34	95	29

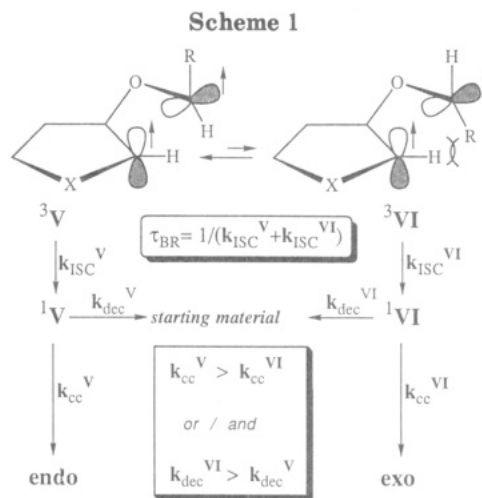
^a In percent, photocycloaddition products in the reaction mixture.

was used because of its high S_1-T_1 intersystem crossing rate and the substantial difference in size between the two substituents at the prostereogenic carbonyl center. The regioselectivity of the 2,3-dihydrofuran (2) photocycloaddition in benzene as solvent was very high (>98:2), leading to the 2,6-dioxabicyclo[3.2.0]heptane as the only detectable regioisomer. The stereoselectivity of this reaction was moderate, yielding an 88:12 mixture of *endo/exo* oxetanes. All other cycloalkenes followed this first observation and preferentially gave *endo* photoproducts, e.g., cyclohexene (4) with a 74:26 *endo:exo* ratio.

Similar results were obtained for the unsubstituted cyclopentene (3), 2,3-dihydropyran (5), 1,4-dioxene (6), and the two dioxolenes 7 and 8 (Table 1).^{29,30} In all cases the *endo* diastereomer was the major photocycloaddition product. For the highly electron rich dioxolene 6 and for cyclopentene this effect was only marginal.

Calculations on several levels of sophistication (MM2 and semiempirical methods AM1 and PM3) of the photoproducts mentioned in Table 1 all assigned the higher heat of formation to the major diastereomer, indicating kinetic control for the product formation. A plausible explanation for this stereoselectivity effect in accordance with the Salem-Rowland rules (*vide supra*) is depicted in Scheme 1: two triplet 1,4-biradical conformers (³V, ³VI) fulfill the necessary prerequisites for ISC to the singlet manifold.

These conformers do not have to represent energy minima but representations of the conformational situations most probable for ISC. The conformational minima preceding these transition points are in rapid



equilibrium with each other with a rate of rotation k_{rot} higher than the rate of intersystem crossing k_{ISC} . Consequently, the lifetime of the biradical (ca. 1–7 ns) is given by the reciprocal sum of the two intersystem crossing rates for the two conformers. The singlet biradicals ¹V and ¹VI should be too short-lived to enable rotation around the endocyclic C–O single bonds, and therefore, conformational memory effects are expected for the photoproducts. Our first assumption²⁹ was that steric repulsion is more critical for the (perpendicular) 1,4-biradical ³VI and depopulation of this conformer is reflected in the higher amount of *endo*-diastereomeric photoadducts (see Table 1) which arise from cyclization of the singlet biradical ¹V via the energetically more favorable triplet ³V. Besides the perpendicularity of the two p-orbitals, a close center to center distance also is crucial for rapid ISC (overlap argument). This requirement also is fulfilled for both conformers ³V and ³VI, and additionally, ³VI suffers more steric repulsions. One way to test this hypothesis was to vary the steric demand of the carbonyl substituent.

Carbonyl Compounds

The simplest way to increase the steric demand of aromatic carbonyl compounds is the introduction of *o*-alkyl groups. We used *o*-tolualdehyde (1e), mesitaldehyde (1f), and the 2,4-di-*tert*-butyl-6-methyl derivative 1g. When irradiated in the presence of 2,3-dihydrofuran (2) (the model cycloalkene for this series), photocycloaddition products were formed in excellent yields with 1e and 1f.³¹

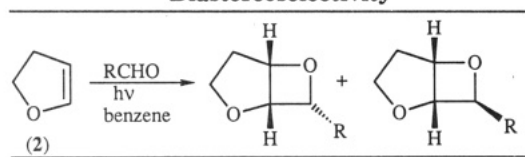
The yield for the Paternò-Büchi adduct from 1g was low (34%) due to rapid intramolecular cyclization (Table 2). Obviously, increase in steric demand by the carbonyl substituent leads to an increase in *endo/exo* stereoselectivity. Additionally, the increasing differences in product stabilities (in favor of the *endo* diastereomer) parallels the increase in stereoselectivity, clearly indicating kinetic control. This trend could also be observed for the reaction of 2,3-dihydrofuran (2) with aliphatic aldehydes 1b–d. These, in diluted solutions, also preferentially react *via* their first excited triplet states. Again, increasing steric demand of the aldehyde substituent leads to an increase in *endo* selectivity.

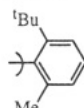
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Table 2. Photocycloaddition of Aliphatic and Aromatic Aldehydes to 2,3-Dihydrofuran: *Endo/Exo* Diastereoselectivity


R =		<i>endo</i> : <i>exo</i>	yield oxetane [a]	ref(s)
methyl	(1b)	45 : 55	44	37
ethyl	(1c)	58 : 42	53	31
isobutyl	(1d)	67 : 33	83	31
phenyl	(1a)	88 : 12	98	30
o-tolyl	(1e)	93 : 7	97	30
mesityl	(1f)	> 98 : 2	90	30
	(1g)	> 98 : 2	34[a]	30
1-naphthyl	(1h)	< 2 : 98	55	37
2-naphthyl	(1i)	< 2 : 98	57	37

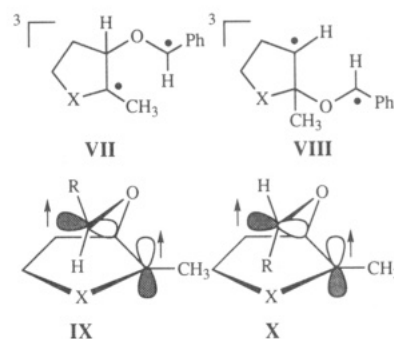
^a Additional 47% benzocyclobutenol formed.

Substituted Cycloalkenes

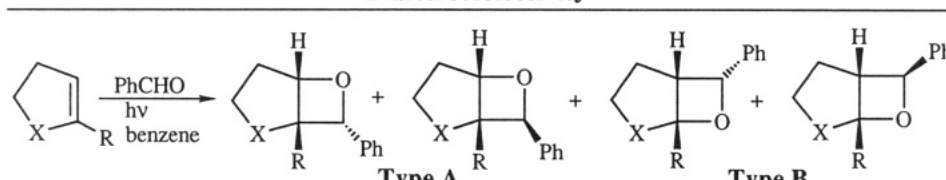
As we have shown for the triplet carbonyl component, increase in steric demand leads to an increase in the amount of thermodynamically less favored *endo* diastereomer. We expected a similar effect to operate also on the cycloalkene side; i.e., substituents at the C-C double bond of the cycloalkenes should enlarge the *endo* selectivity. It was of no little surprise to notice that this is not the case (Table 3).³³

For all systems investigated, the *endo:exo* ratios dropped and for specific regioisomers even an *exo* selectivity of 80–84% could be observed. Illustrative is the photocycloaddition of benzaldehyde with 5-methyl-2,3-dihydrofuran (9): the extra 5-methyl group

exhibits a stabilizing effect on the ring-localized carbon radical of the triplet biradical (VII), thus inducing high regioselectivity for the primary addition step. Apparently this was the case and only one regioisomer could be detected. The 88:12 diastereomeric ratio for the 2,3-dihydrofuran (2) case, however, decreased to a 65:35 ratio for 9. This effect was even more impressive for the 1-methylcyclopentene (10) type A regioisomers. Clearly the second reaction event, the combination of the two radical centers, is responsible for this effect. This drastic selectivity decrease, however, was not observed for the type B regioisomeric oxetanes which were formed from 1-methylcyclopentene (10) or 1-methylcyclohexene (11). Here the second reaction event must be the recombination of the α -oxo-radical center with the unsubstituted ring carbon radical in a triplet biradical with structure VIII. These regioisomers were formed with nearly the same diastereoselectivity as observed for the unsubstituted cycloalkene counterparts.



Steric repulsion is responsible for the *endo* selectivity of the latter compounds. These repulsions run parallel with increasing size of the carbonyl substituent R, thus reflected in increasing *endo:exo* ratios (see Table

Table 3. Photocycloaddition of Benzaldehyde to Methyl-Substituted Cycloalkenes: Regioselectivity and *Endo/Exo* Diastereoselectivity


X =	R =	<i>endo</i> : <i>exo</i>	rel yield [a]	<i>endo</i> : <i>exo</i>	rel yield [a]
O	H (2)	88 : 12	> 98		
	CH ₃ (9)	65 : 35	> 98		
CH ₂	H (3)	61 : 39	-	61 : 39	-
	CH ₃ (10)	16 : 84	49	49 : 51	51
(CH ₂) ₂	H (4)	74 : 26	-	74 : 26	-
	CH ₃ (11)	67 : 33	52	66 : 34	48

X =	<i>endo</i> : <i>exo</i>	yield
CH ₂ (12)	20 : 80	48
(CH ₂) ₂ (13)	44 : 56	60

^a Relative proportions of regioisomers, by NMR spectroscopy.

2). If the cycloalkene part bears substituents at one of the two sp^2 carbons, the conformers 3V and 3VI (Scheme 1, out of plane approach of the carbonyl compound) are no longer the only ones to be considered.³³ As long as only biradicals of type **VIII** are concerned (leading to type B regioisomers), no substantial differences in stereoselectivity should be expected. The triplet biradicals of type **VII** (leading to type A regioisomers), however, suffer from increasing gauche interactions between methyl substituents at the cycloalkene and the β -alkoxy substituent. Therefore conformers 3IX and 3X have to be additionally considered. Following the argument given for 3V and 3VI , because of steric reasons, preferentially the biradical 3IX is converted into the photoproduct, but in this case, the *exo* selectivity. The experimental data for this type of product (clearly indicated for the products from **12** and **13**) constitute a balanced situation between all biradical conformers **V**, **VI**, **IX**, and **X**.

State Selectivity: Singlet Excited Carbonyl Compounds

Due to rapid intersystem crossing from S_1 , the aromatic carbonyl compounds used for the investigation of product stereoselectivity reflected "pure" $T_1(n\pi^*)$ photochemistry.³⁴ The corresponding aliphatic carbonyls have a k_{ISC} about 10-fold lower and therefore they can react from S_1 as well as T_1 .³⁵ Addition of triplet quenchers moderates the reactivity pattern. Using cyclohexene (**5**) as starting material and acetaldehyde (**1b**) as carbonyl addend in the presence and absence of a triplet quencher (1,3-pentadiene), different *endo:exo* ratios were obtained. The amount of *endo* diastereomer decreased with increasing amounts of triplet quencher. This indicates that the reaction via the triplet biradical is highly *endo* selective in contrast to the analogous reaction via singlet excited acetaldehyde. A similar correlation of oxetane stereoselectivity with the nature of the electronic state of the aldehyde was made by Jones.³⁶ On the other hand, some aromatic carbonyl compounds have low-lying triplet $\pi\pi^*$ states and predominantly the rather short-lived $S_1(n\pi^*)$ state exhibits the typical carbonyl photochemistry.³⁷ Examples investigated were the α - and β -naphthaldehydes (**1h,i**).³⁸ The steric demand of the naphthyl substituent is comparable to the substituents in **1e** or **1f**. In contrast to these substrates, however, the naphthaldehydes **1h,i** (a) gave cycloadditions also in the presence of triplet quenchers, (b) showed fluorescence quenching in the presence of cycloalkenes, and (c) exhibited high *exo* diastereoselectivity (see Table 2). With 2,3-dihydrofuran (**2**) only the *exo* diastereomer was observed, the structure of which was established by X-ray analysis.³⁸ Obviously, singlet excited naphthaldehydes add to cycloalkenes with high *exo* selectivity and with formation of the thermodynamically more favored diastereomers.

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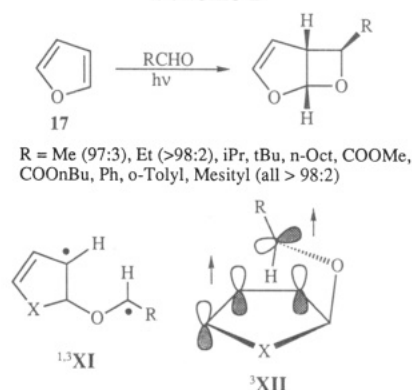
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Table 4. Photocycloaddition of Benzaldehyde to Dioxolenes: *Endo/Exo* Diastereoselectivity

R=	R' =	R'' =	endo : exo	yield oxetane [a,b]
Me	H	H (7)	52 : 48	83
iPr	H	H (8)	66 : 34	95
Me	Me	H (14)	22 : 78	90
H	Me	Me (15)	48 : 52	63
Me	Me	Me (16)	<10 : 90	30

^a Equimolar amounts of aldehyde and dioxolene. ^b In percent, photocycloaddition products in the reaction mixture.

Scheme 2



The Role of Photo Electron Transfer Processes (PET)

Nonpolar solvents such as benzene or cyclohexane were used in our investigations in order to suppress strong solute-solvent interactions. Applying the Rehm-Weller equation³⁹ and using the oxidation potentials of different cycloalkenes⁴⁰ led to the result that in nonpolar solvents photoelectron transfer (PET) from cycloalkenes to benzaldehyde should be thermodynamically feasible ($\Delta G < 0.1$ eV) only for dimethyl-substituted dioxolenes **15** and **16**. The product ratios should reflect this trend and exhibit pronounced differences compared with the carbocyclic olefins and enol ethers (Table 4).

The 4-methyl-substituted dioxolene **14** gave rise exclusively to one regioisomer similar to the 2,3-dihydrofuran (**2**) case, indicating the biradical reaction path operating. In contrast to this, the tetrasubstituted dioxolenes **15** and **16** showed a strong dependence of the *endo:exo* ratios on the substituents at the C-2 position. Despite the sterically demanding isopropyl substituents at C-2 compound **8**, 66% of the *endo* diastereomer was formed, whereas methylation of position C-4 in compound **14** is enough to increase *exo* selectivity. In cases **15** and **16** diphenylethylene glycol was formed as the major side product (for **16** even the main reaction product), thus indicating the formation of the benzaldehyde radical anion via an electron-transfer step. Therefore we assume PET to be an important competing process⁴¹ in the case of these cycloalkenes.

1,3-Cyclodienes

A special case is the Paternò-Büchi reaction with furan (**17**) (Scheme 2), which already exhibits maximum

regio- and (*exo*)stereoselectivity (>98:2) for simple aliphatic aldehydes,⁴² in contradiction to our reaction model, which predicts *endo* selectivity. Obviously this is a situation which also can be observed for other heterocyclic olefin compounds such as thiophenes or oxazoles and many more.⁴³ A secondary orbital effect can be postulated for these reactions; however, it is not clear at what stage this effect operates. A stabilized singlet biradical ¹XI could be proposed with a lifetime long enough to allow bond rotations and thermodynamic product control.

There are several examples for long-lived *singlet* 1,4-biradicals of the "non-Kekulé" type in the literature.⁴⁴ The exceedingly high diastereoselectivity which is (for most cases) independent of the substituents on the 1,3-cycloaddition and even independent of the electronic state of the carbonyl compound, however, could hardly be explained by this assumption. If one takes into account the prerequisites (*vide supra*) for rapid ISC, an interaction between the rather flexible α -oxy radical center with the allyloxy ring localized radical in ³XII is likely to play a major role. The resulting conformer should give, with exceedingly high stereoselectivity, the *exo* diastereomer via ¹XII. The latter biradical already exhibits the proper orientation for bond formation. This picture, however, implies that steric interactions play a much more decisive role here due to the near perpendicular arrangement of the α -C₁H bond and the ring plane. Any increase in steric demand should therefore lead to (a) an immediate switch to biradical conformers of the type V and VI (as depicted in Scheme 1) and (b) a decrease in stereoselectivity. This pre-

diction was confirmed by preliminary experiments in our laboratory: whereas benzaldehyde gave a >98:2 *exo* (phenyl) selectivity with furan, phenyl pyruvic esters led to diastereomeric mixtures with the *endo* (phenyl) isomer >90% preferred.⁴⁵

Conclusions

Our results suggest that the relative configuration of photoproducts reflects the molecular geometry prior to the ISC process and therefore constitutes a "memory effect". As indicated in Scheme 1, bond formation between the two carbon radical centers, however, is not the only possibility for deactivation of the singlet biradicals ¹V and ¹VI. C–O bond cleavage can occur in competition with C–C bond formation. If the radical centers in a triplet 1,4-biradical are separated in space more than approximately 3 Å and additional rotation around the central (2–3) single bond is necessary to enable bonding interaction, the retrocleavage pathway should be preferred.⁴⁶ Temperature effects on this subtle interplay between bond formation and bond cleavage have been intensively investigated by Scharf and co-workers and used for the determination of isoinversion points.⁴⁷ All arguments concerning steric effects in biradical conformers should also hold true for this second possibility. Therefore a clear-cut selection between events at the triplet stage or at the singlet stage is problematic as long as exact data on triplet lifetimes of the preoxetanes do not exist.

Wagner and co-workers have determined triplet lifetimes of 1,5-biradicals generated by δ -hydrogen abstraction using the cyclopropylcarbinyl radical clock.⁴⁸ For these cases no pronounced correlation between lifetimes and p orbital alignment could be observed; i.e., triplet biradicals with much different orbital orientations decay at nearly the same rate. The authors attributed this result to the degree of orbital overlap that provides SOC and the surface crossing required for rapid ISC. We consider both orbital alignment and overlap crucial for the stereochemical result of the photoreaction and feel that both factors are in agreement with our results. In addition to these considerations, pyramidalization of the spin-bearing atoms could promote ISC and also contribute as a selectivity controlling factor.⁴⁹ In summary, the already postulated⁵⁰ correlation between product structure and ISC geometries ("memory effects") is reflected in our results quite convincingly. To further substantiate this correlation, reactions should be investigated which are already known to proceed with high regio- and diastereoselectivity.⁵¹ Substituent variation with concomitant triplet lifetime determination by flash spectroscopy or by radical clocks would be a valuable concept to clarify the influence of biradical structure on product selectivity.

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