The Link Between Stereoselectivity and Spin Selectivity in Intermolecular and Intramolecular Photochemical Reactions

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How stereoselectivity in singlet and triplet photocycloaddition and photocyclization reactions, respectively, is linked to spin selectivity and how this link affects our understanding of photochemical reaction mechanisms, is described in this review. As illustrative examples, the Paternò-Büchi reaction and the Norrish-Yang cyclization are described with emphasis on triplet biradical structure and dynamics.

key words: photochemistry, biradicals, spin selectivity, stereoselectivity, Paternò-Büchi reaction, Yang reaction, photocycloaddition, photocyclization

INTRODUCTION

Spin chemistry is an innovative new research area in photochemistry [1]. Applications designed for organic synthesis are rare - the basic phenomena, however, are known since decades. The key feature of all processes in the context of the spin chemistry phenomena is the spin conservation rule ($\Delta S = 0$). Specifically, bond forming or bond breaking processes are strictly spin-forbidden when coupled with a change in spin multiplicity of one molecule or a set of strongly coupled molecules (a ground-state complex or an exciplex). Spin chemistry, however, exists only as an interesting concept and is transformed into real world because this rule is **not** strictly observed and mechanisms exist which allow spin flips coupled with chemical reactions.

The vast majority of organic molecules exist in singlet electronic ground states and there are no spin restrictions for either unimolecular processes or bimolecular reactions with other singlet molecules. In the case of mono-radical additions to organic substrates in their singlet electronic ground states, no spin restrictions exist and doublet states are generated which can propargate in chain reactions. A multitude of 1,n-biradicals with triplet multiplicity originate from triplet/singlet interactions in photochemical reactions and these triplet biradicals have been extensively studied in the last decades both spectroscopically and theoretically. They can be formed in an intermolecular fashion thus representing the first step of photoaddition reactions or intramolecularly in photocyclizations. These intermediates are the direct consequence of the precursor spin and their lifetimes are connected with the mode of spin inversion processes and mechanisms, which

lead to the formation of closed-shell products. As depicted in Figure 1, an interesting question concerns what the optimal geometries are for efficient crossing from the triplet to the singlet PES and how this crossing geometry is connected to both the constitution and (for productive reactions) relative configuration, i.e. the stereochemistry, of the closed-shell products.

Photochemistry is especially valuable when applied to the synthesis of target molecules which are less readily available by thermal or other methods. Furthermore, selectivity has become the most important feature in synthetic organic chemistry since several decades. As far as ground state chemistry is concerned, chemo-, regio-, and stereoselectivity are the essential factors which determine the success and the usefulness of a reaction. Photochemistry makes an additional possibility available, i.e. spin-selectivity, which has been long known and studied for many photochemical model reactions. Notwithstanding, it should be emphasized that spin-selectivity allows the modification of a chemical reaction solely by taking advantage of the different lifetimes and reactivities of two (or more) electronically excited states of the same molecule (spin-isomers).

Triplet states $^3A^*$ could be selectively generated by triplet-triplet energy-transfer (sensitization) and selectively deactivated by quenching. The latter process allows the study of the singlet state $^1A^*$ behavior in chemical transformations. The
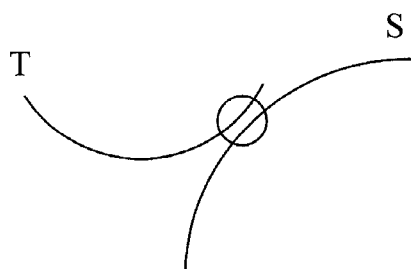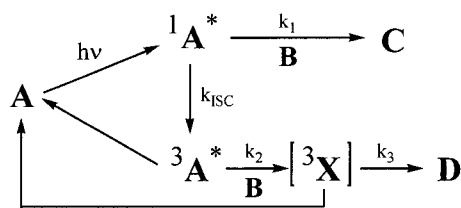

Figure 1.

Scheme 1.

mechanistic scenario shown in Scheme 1 implies that two different products **C** and **D** arise from the respective spin isomers $^1A^*$ and $^3A^*$. This effect can be expressed simply by a process, in which the triplet intermediate ^3X returns to the substrate after inter-system crossing (ISC) while the singlet intermediate $^1A^*$ reacts with **B** to give the product molecule **C**. Alternatively, two constitutionally different products **C** and **D** can be formed (like for example in oxa-di-π-methane rearrangements) or **C** and **D** constitute two diastereoisomers. The later case is especially interesting because spin-multiplicity does not only influence the reactivity of the excited molecules (due to energy and lifetime effects), but it also alters the regio- and stereoselectivity of the product-forming steps. In singlet photoreactions, stereoselectivity is often controlled by the optimal geometries for radical-radical combinations, whereas in triplet photoreactions the geometries most favorable for intersystem crossing (ISC) are considered to be of similar relevance. These geometries can be quite different from the former ones due to differences in spin-orbit coupling (SOC) values. These aspects play a crucial role for two important photochemical reactions for the synthesis of small-ring products (Scheme 2) : the *Paternò-Büchi* reaction [2], and the *Norrish-Yang* photocyclization [3]. 1,4-Triplet biradicals are crucial intermediates in the triplet versions of these reactions. They have been detected by spectroscopy, trapping experiments or radical clock experiments. The lifetime of these species is in the nano- up to microsecond region which gives enough time for molecular motions, especially bond rotations, which are normally not available for their singlet spin-isomers. Thus, the conservation of configuration when going from the starting material to the product is no longer expected for triplet
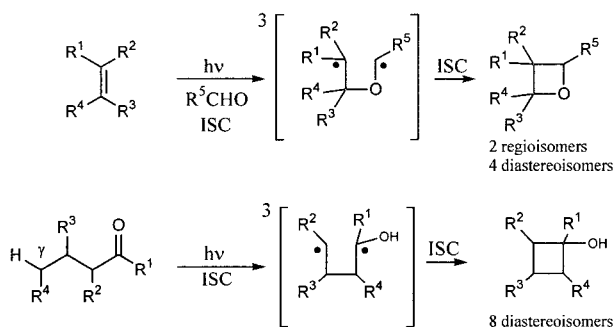
photoreactions and stereochemistry can be used as a simple tool for differentiation between these two reaction channels. The isomeric singlet biradicals have been detected only in the last two decades and are extremely short-lived if not highly stabilized by spin-diluting substituents.
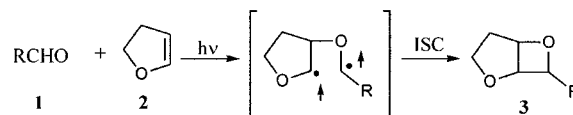
We were interested in the question whether the "simple" diastereoselectivity (in contrast to the induced diastereoselectivity - or asymmetric induction) is coupled to spin-selectivity or not. In order to investigate this question in a systematic fashion, we have studied combinations of simple model substrates in the Paternò-Büchi reaction and in the Norrish-Yang cyclization.
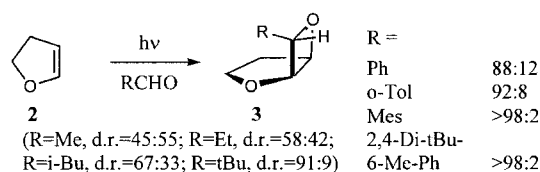
DISSCUSION

The Carbonyl-Ene Photocycloaddition. First approach

In order to separately analyze facial and simple diastereoselectivity and the termination step of the Paternò-Büchi reaction, we investigated as model substrates simple unfunctionalized cycloalkenes. As carbonyl addends prochiral aldehydes (1) were applied. The most intensively investigated alkene was 2,3-dihydrofuran (2), which gave the Paternò-Büchi product 3 with high (98:2) regioselectivity (Scheme 3) [4].

The regiochemical aspect of the Paternò-Büchi reaction is often discussed in terms of the "most stable biradical rule". This rule, however, ignores that the approach geometry between the electronically excited carbonyl and the alkene component does not necessarily have to result in the energetically more stable 1,4-biradical. Exciplexes with strong charge transfer character have not yet been detected in the Paternò-Büchi reaction but solvent effects account for several different regioselectivity-determining factors. In nonpolar solvents the photocycloadditions proceeded with good chemical yields and surprising diastereoselectivities. The DHF-addition to acetaldehyde (both substrates applied in 0.2 M concentrations) resulted in a 45 : 55 mixture of *endo* and *exo* diastereoisomers 3 (Scheme 4). With increasing size of the α-carbonyl substituent (Me-Et-iPr-Ph-tBu), the simple diastereoselectivity increased, favouring formation of the *endo* stereoisomer. The benzaldehyde

Scheme 3.

Scheme 2.

|	R =	
	Ph	88:12
	o-Tol	92:8
	Mes	>98:2
	2,4-Di-tBu-	
(R=Me, d.r.=45:55; R=Et, d.r.=58:42; R=i-Bu, d.r.=67:33; R=tBu, d.r.=91:9)	6-Me-Ph	>98:2

Scheme 4.

addition, which was most intensively investigated, gave a 88 : 12 mixture of *endo* and *exo* diastereoisomers. Thus, the thermodynamically less stable stereoisomers (>1.5 kcal/mol, *ab initio* calculations) were formed preferentially. In order to enlarge the phenyl substituent, we used ortho-tolyl- and mesitylaldehyde as well as 2,4-di-*tert*-butyl-6-methyl benzaldehyde and actually the diastereoselectivity did further increase [5].

No trace (>99.5 : 0.5 by NMR) of the *exo* diastereoisomer was found in the Paternò-Büchi reaction of the latter carbonyl reagent. This contrathermodynamic trend was also found with other cycloalkenes such as 2,3-dihydropyran, cyclohexene, cyclopentene and cyclobutene (Scheme 5).

Especially interesting alkenes were 1,3-dioxolenes because additional differentiation between the two sites of the molecule could be achieved by variation of the substituents at the acetal center C-2. In agreement with the results described above, an increase in steric demand of one of the α-substituents led to an increase in *endo*-selectivity. The photocycloaddition of benzaldehyde to 2,2-*bis*-isopropyl-1,3-dioxolene (**4**) resulted in a 65 : 35 *endo/exo*-mixture of oxetanes **5** (Scheme 6). Again, an increase in steric demand of the α-substituent at the carbonyl component improved the *endo/exo*-ratio. Methyl trimethylpyruvate (**6**) with the sterically more demanding *tert*.-butyl group gave solely the *endo*-diastereoisomeric oxetane (d.s. >98%) **7** with the dioxolene substrate **4** [6]. In accord with these results were also the simple diastereoselectivities described by for the ethyl phenylglyoxylate photocycloadditions (i.e. *endo* phenyl selectivity) with cyclopentene, cyclohexene, 2,3-dihydropyran and 1,3-cyclohexadiene [7]. In all cases, exclusively the *endo*-phenyl diastereoisomers were formed. Again, these products were less stable (0.5-1.0 kcal/mol) than the corresponding *exo*-diastereoisomers which were not detected.

Most of the results described above were striking in the sense that classical textbook analysis of triplet photocycloaddition reactions leads to a completely different expectation.
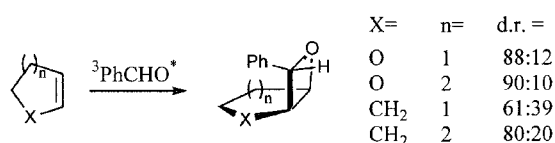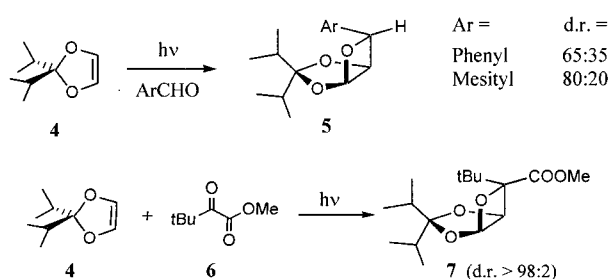
The lifetimes of many triplet biradical intermediates (trime-thylenes, tetramethylenes or 2-oxa-tetramethylenes) [8] are definitely high enough to enable bond rotations. Thus, formation of the thermodynamically favoured product can be expected because the radical-radical combination step should no longer be influenced by the approach geometry, i.e. "memory effects" should be erased due to the relatively long lifetimes. On the other hand, converting triplet biradical to closed shell products means intersystem crossing which is a spin-forbidden process and requires special geometric and energetic conditions. These criteria were described for the first time in the legendary publication by Salem and Rowland, emphasizing the role of spin-orbit coupling (SOC) as the decisive interactive mechanism for triplet to singlet intersystem crossing in 1,n-biradicals [9]. In contrast to other interactions such as electron-nuclear hyperfine coupling (HFC) and spin-lattice relaxation (SLR), SOC strongly depends on the geometry of the triplet biradical. The rules postulated in the paper by *Salem* and *Rowland* were: (i) SOC decreases with increasing distance between the two spin-bearing atoms (because of additional through-bond interactions in the 1,n-biradical, not only is the actual distance between the two radical centers important but also the number of bonds (n-1)); (ii) conservation of the total angular momentum demands that the axes of the p-orbitals at the radical centers are oriented orthogonal to each other and these in turn mutually orthogonal to the axes around which the orbital angular momentum is changed; and (iii) SOC is proportional to the ionic character of the corresponding singlet biradical state. Based on these three rules, a pronounced conformational and structural dependence should result for the lifetime of triplet 1,n-biradicals.

A numerical equation for SOC was reported by Carlacci and Doubleday *et al.*: SOC = B(R) |S| sin φ (Figure 2) [10]. B(R) is a function of the distance R between the radical centers, φ the angle between the localized p-orbitals at these positions and |S| the overlap integral of these orbitals. Spin-orbit coupling (SOC) controls the rate of ISC for tetramethylene, 2-oxatetramethylene or trimethylene triplet biradicals, i.e. strong SOC enhances the ISC-rate and lowers the lifetime of the triplet biradicals. The spatial orientation of the two singly occupied orbitals has been determined to be highly important

X=	n=	d.r. =
O	1	88:12
O	2	90:10
CH₂	1	61:39
CH₂	2	80:20

Scheme 5.

Ar =	d.r. =
Phenyl	65:35
Mesityl	80:20

Scheme 6.

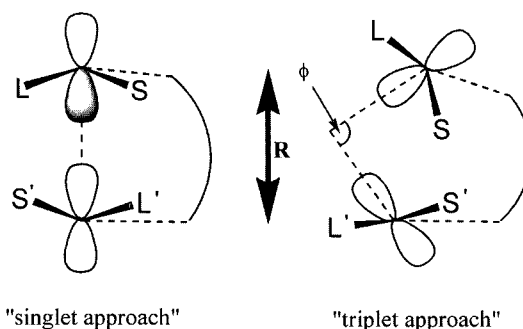"singlet approach"   "triplet approach"

Figure 2.

for the biradical lifetimes, whereas the through-space distance between the radical centers plays a subordinate role and the degree of ionic contribution in the corresponding singlet state often seems to be overestimated. This clearly indicates that for flexible 1,4-triplet biradicals not only one conformational arrangement is responsible for facilitating ISC, but many. After transition from the triplet to the singlet potential energy surface, immediate product formation is expected. *Thus, ISC is expected to proceed concerted with the formation of a new bond or the cleavage of the primarily formed single bond.* As long as we are interested in high product stereoselectivity and not in the quantum yields of product formation, only tight biradical geometries must be considered as relevant for biradical coupling. The reactive conformers do not have to be energy minima but conformational situations most probable for triplet-singlet interconversion (Scheme 7).

The conformational minimum structures 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 triplet biradical (ca. 1-7 ns for 2-oxatetramethylenes) [11] is given by the reciprocal sum of the two intersystem crossing rates for the two "tight" conformers and the ISC-rate for *anti*-conformers (which have, however, substantially lower SOC-values) [12]. The transition can directly produce a vibrationally hot ground-state of the product or a longer-lived singlet 1,4-biradical with low bond-order between the radical centers. The latter possibility might exist for highly stabilized (allylic or benzylic) 1,n-biradicals which have already been reported in the literature. Be it as it may, the singlet biradicals should be too short-lived to enable rotation about the endocyclic C-O or C-C bonds and therefore, conformational memory effects on the stereochemistry of the products are expected. This situation is depicted for the Paternò-Büchi reaction of a triplet excited RCHO with a five-membered cycloalkene. Minimization of steric interaction between the substituents at the terminal centers favours structure syn-^3A over syn'-^3A which collapses after ISC to give the *endo*-diastereoisomer in competition to the cleavage reaction. During the formation of the second C-C-bond, steric interaction
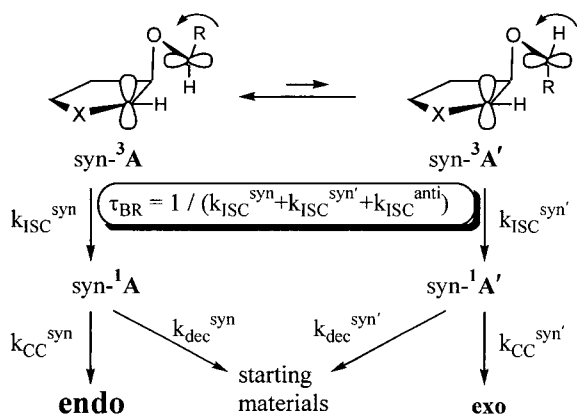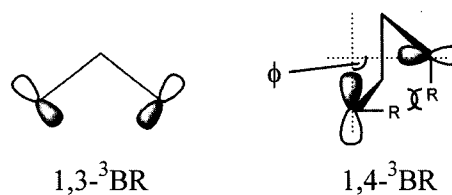
increases between the ring skeleton atoms and the substituent R which might also favour the turn-off into the cleavage channel. Thus, the stereoselectivity of the Paternò-Büchi reaction as well as of any other reaction, involving triplet 1,n-biradicals (with n>3) is the result of a combination of several rate constants for cyclization *versus* cleavage reactions. This model led to a series of predictions. Firstly, in a triplet 1,3-biradical, steric interactions between substituents at C-1 and C-3 are continuously increasing during bond formation because the maximum value for sin ϕ is obtained for an in-plane conformation of the p-orbitals and therefore no contrathermodynamic effect is expected. Quite contrary the situation for a triplet 1,4-biradical (Figure 3).

If 1,4-singlet biradicals 1,4-^1BR are interpreted as representations for extremely short-lived intermediates in asynchronous [2+2]-photocycloadditions, a strong preference for the formation of least-strained (*trans*) products is reasonable. The orthogonal alignment in 1,4-^3BR in the SOC-reactive conformers leads to a "masochistic" substituent effect in that the sterically demanding groups R tend to align *cis* during the bond formation step (Figure 4).

Thus, we predicted a pronounced switch in diastereoselectivity when going from triplet to singlet excited carbonyl compounds in Paternò-Büchi reactions with the same alkene substrates but not for 1,3-photocyclization reactions. Secondly, we expected that alkylation of the unsubstituted site of the double bond in cycloalkenes or double steric crowding of one
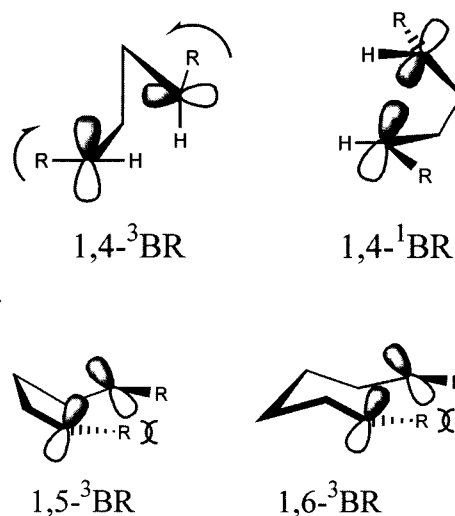

1,3-^3BR 1,4-^3BR

Figure 3.

1,4-^3BR 1,4-^1BR

Figure 4.

1,5-^3BR 1,6-^3BR

Figure 5.

syn-^3A syn-$^3A'$

$$k_{ISC}^{syn} \left[\tau_{BR} = 1 / (k_{ISC}^{syn} + k_{ISC}^{syn'} + k_{ISC}^{anti}) \right] k_{ISC}^{syn'}$$

syn-^1A syn-$^1A'$

k_{CC}^{syn} k_{dec}^{syn} $k_{dec}^{syn'}$ $k_{CC}^{syn'}$

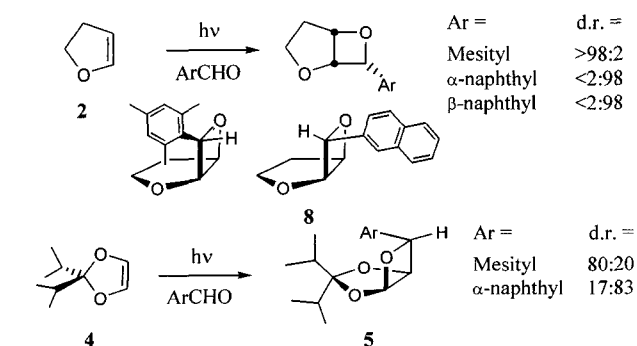**endo**   starting materials   **exo**

Scheme 7.

at the biradical termini should lower the stereoselectivity and might even invert the *endo/exo*-ratio. Thirdly, the basic idea of p-orbital orientation must also be valid for 1,5- and 1,6-biradicals, albeit these intermediates are conformationally much more flexible species (Figure 5).

Second approach

Additionally to the results described for "simple" substrate combinations, we obtained further mechanistic implications from more complex starting materials: (a) substituents at the cycloalkenes which we originally used as substrates unsystematically influenced the stereoselectivity, e.g. in 2,3-dihydrofuran, methylation at C-5 reduced the *endo/exo*-ratio strongly, whereas C-2,5-dimethylation of furan did not change the high *exo/endo*-selectivity, (b) cycloalka-1,3-dienes as well as five-membered aromatics were highly *exo*-selective in contrast to the corresponding cycloalkenes, (c) an increase in solvent polarity led to an decrease in regioselectivity as well as an inverted diastereoselectivity in the "new" regioisomer, (d) the stereoselectivities showed strong dependence on the substrate concentration and unusual temperature dependence. These results can be discussed in terms of multiplicity, substituent, electron transfer, secondary orbital, concentration, and temperature effects:

Multiplicity Effects

Whatever the mechanism is for the corresponding singlet photoreactions, ISC-geometries cannot be of relevance. Thus, if singlet and triplet photocycloadditions with identical chemo- and regioselectivity are compared, the differences in diastereoselectivities allow a conclusion about the role of ISC geometries. Naphthaldehyes can be used in Paternò-Büchi reactions as singlet excited carbonyl components [13]. The reaction efficiencies and chemical yields are normally much lower compared to other aromatic ketones or aldehydes, but chemo- and regioselectivities are often identical. The Paternò-Büchi reaction of 2-naphthaldehyde with 2,3-dihydrofuran (2) is a singlet process (as shown by triplet sensitization experiments) and gives exclusively the *exo*-diastereoisomer 8 (Scheme 8).

Similar results were obtained for the 2,2-*bis*-isopropyl-1,3-dioxolene (4): the *endo/exo*-ratio is inverted for the oxetane 5 when going from the triplet excited mesitylaldehyde to the singlet excited naphthaldehyde as substrate. The comparison of these experiments with the benzaldehyde cycloadditions reveals the role of ISC-geometries in triplet photocycloadditions.
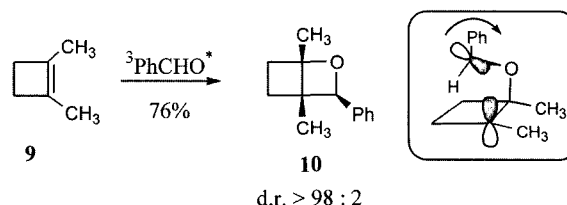
Substituent Effects

Two structural features made the conformational analysis of spin-inversion geometries straightforward: the two sites of the alkene part were well differentiated concerning the degree of substitution and steric hindrance. The alkenes investigated were always cyclic, thus reducing the conformational flexibility at the biradical stage. The situation became more complex when one or both of these structural features is modified. Methyl-substituted cycloalkenes have two ISC-reactive sites and thus, the *endo/exo*-ratios drop significantly [14]. An extreme example was 1,2-dimethylcyclobutene (9): the Paternò-Büchi reaction of this substrate with benzaldehyde resulted solely in the *exo*-diastereoisomer 10 (Scheme 9).
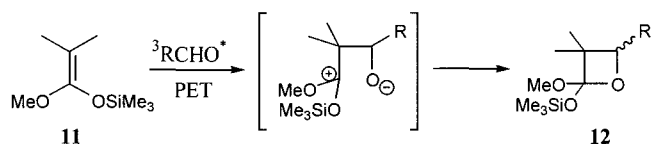
This is exactly predicted by the ISC-geometry model, because the *bis*-methylated site of the cycloalkene is now sterically more demanding (compared to unsubstituted starting materials) and the biradical combination trajectory involves the approach from the less shielded cyclobutene plane. Steric hindrance can also reach a critical value during bond formation and might favor the formation of the thermodynamically stable product. In a report by *Park* and his coworkers the photocycloaddition of benzaldehyde to 2,2-diethoxy-3,4-dihydro-2H-pyran is described and this process gave preferentially the *exo*-phenyl product (d.e. 92%) [15].

Electron Transfer Competition

Another feature, which might oppose the ISC-geometry model is primary photoinduced electron transfer (PET). If this process is energetically feasible, the geometric restrictions might be circumvented, i.e. intersystem crossing can occur at the stage of the radical ion pair and a singlet 1,4-biradical or a 1,4-zwitterion can be formed depending on the reaction conditions. In polar solvents, the assumption of a 1,4-zwitterion as decisive intermediate is reasonable. Both regio- and diastereoselectivity are influenced by this mechanistic scenario. The regioselectivity is now a consequence of maximum charge stabilization and no longer a consequence of the primary interaction between excited carbonyl compound and alkene.

Ar =	d.r. =
Mesityl	>98:2
α-naphthyl	<2:98
β-naphthyl	<2:98

Ar =	d.r. =
Mesityl	80:20
α-naphthyl	17:83

Scheme 8.

d.r. > 98 : 2

Scheme 9.

Scheme 10.

d.r. > 90:10 for
X = CH_2, $(CH_2)_2$, O, S, NR
R = Alkyl, Aryl, R CO

Scheme 12.

Whereas 3-alkoxyoxetanes are preferentially formed from triplet excited aldehydes and enolethers, 2-alkoxyoxetanes **12** result from the reaction of triplet excited ketones or aldehydes and highly electron-rich ketene silylacetals **11** (Scheme 10) [16].

In the latter case, photoinduced electron transfer (PET) to give the carbonyl radical anion and the ketene acetal radical cation is energetically feasible. PET might be followed by ISC and formation of a highly stabilized 1,4-zwitterion intermediate (aldol-intermediate). Eventually, C-O bond formation leads to the oxetanes **12** with correct (with respect to the experimental results) regiochemistry. Substituent tuning is not the only possibility to influence the regioselectivity of the Paternò-Büchi reaction. By processing the photocycloaddition in a highly polar solvent which reduces the Coulombic term in the Rehm-Weller equation [17], PET became compatible with radical pathways. This effect was observed with 2,3-dihydrofuran (**2**) as electron-rich substrate which gave selectively the 3-alkoxyoxetane **3** when reacted with triplet excited aliphatic aldehydes in nonpolar solvents (Scheme 11).

In acetonitrile, however, also the corresponding 2-alkoxyoxetane **13** was detected. The relative amount of this product correlated with solvent polarity parameters thus indicates PET as the responsible mechanism. If a 1,4-zwitterion is formed during the reaction, the stereochemistry is no longer controlled by ISC-geometries but by the orientation of the two prostereogenic carbon centers of the radical ions when forming the primary C-C-bond. The major diastereoisomer obtained from the PET-cycloaddition of benzaldehyde with 2,3-dihydrofuran was the *exo*-phenyl isomer (d.r. 85 : 15). Thus, a switch from 1,4-biradical to 1,4-zwitterion path leads to an inversion of regio- and diastereoselectivity. A mechanism, which involves a sequence of PET, formation of a contact ion pair and charge recombination to give a triplet 1,4-biradical [18], also explains the change in regioselectivity. This is due to the different orientation of radical anion and radical cation in the CIP) but is in contradication to the observed diastereoselectivity
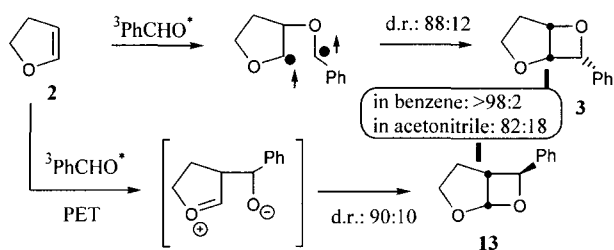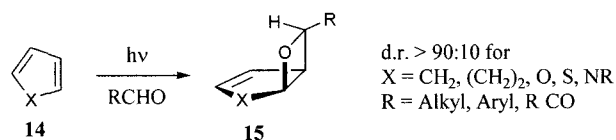
(15 : 85 *endo/exo*-ratio), which should also favour formation of the *endo*-phenyl isomer from the alternative 1,4-triplet biradical (similar as for the biradical collapse from the cyclopentene/benzaldehyde reaction (61:39 *endo/exo*-ratio).

Carbocyclic and heterocyclic dienes

At first sight, a remarkable exception to the stereodirecting rules discussed above exists for an exceedingly important class of alkene-substrates for Paternò-Büchi reactions. These are furan and furan derivatives as well as other heteroaromatic substrates such as thiophenes, pyrroles, imidazoles, and thiazoles and even carbocyclic dienes such as 1,3-cyclopentadiene or 1,3-cyclohexadiene [19]. The photocycloaddition of these 1,3-dienes **14** with aromatic and aliphatic aldehydes proceeds with unusually high *exo*-diastereoselectivity to give the bicyclic oxetanes **15** in good yields (Scheme 12). For most examples, no exact d.r. values are reported in the literature, however, the *exo*-diastereoselectivity definitely exceeds 90% in all cases.

We have investigated the Paternò-Büchi reaction of furan (**16**) with acetaldehyde and with benzaldehyde [17]. The diastereoselectivities (*exo/endo*-ratios) were 82 : 1 and 212 : 1. Thus, the extraordinary high stereoselectivity of the benzaldehyde/furan photocycloaddition is not a result of π-interactions with the phenyl substituent. It was therefore of interest to study the influence of α-substituents in benzoyl compounds on the stereoselectivity of the Paternò-Büchi reaction with furan. Surprisingly, the exchange of the hydrogen in benzaldehyde by a methoxy group completely inverts the diastereoselectivity in the photocycloaddition with furan. Further modification of the α-substituent in the benzoyl substrates uncovered a distinct dependence of the *exo/endo*-ratio on the size of this substituent. The acetophenone reaction with **16** gave only one product, whereas a 77 : 23 mixture of diastereoisomers **17/18** resulted from the addition of benzoyl cyanide. Increasing the size of the aroyl cyanide aryl group from phenyl to mesityl led to an increase in *exo*-diastereoselectivity from 3.9:1 to 16 : 1.[27] Thus, by changing the α-substituent from H or Me to CN, COOMe, OMe and eventually COOR, the direction (*exo*-phenyl versus *endo*-phenyl) of the diastereoselectivity was completely switched (Scheme 13) [17].

Again, this cannot be a result of π-interactions with the phenyl substituent, because an identical sequence was obtained when using the corresponding *tert.*-butyl compounds, i.e. pivaldehyde gave solely the *exo* [2+2] cycloadduct, whereas methyl trimethylpyruvate exclusively resulted in the formation of the *endo* [2+2] cycloadduct (*exo, endo* with respect to the *tert.*-butyl group). What might be the reason for this peculiar
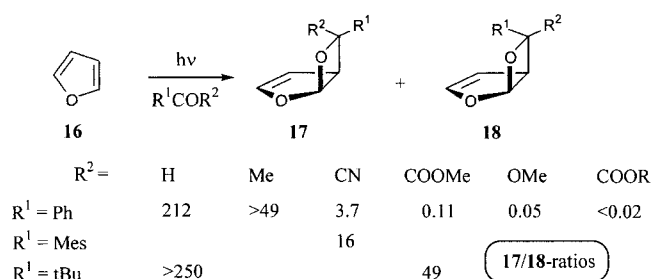
Scheme 11.
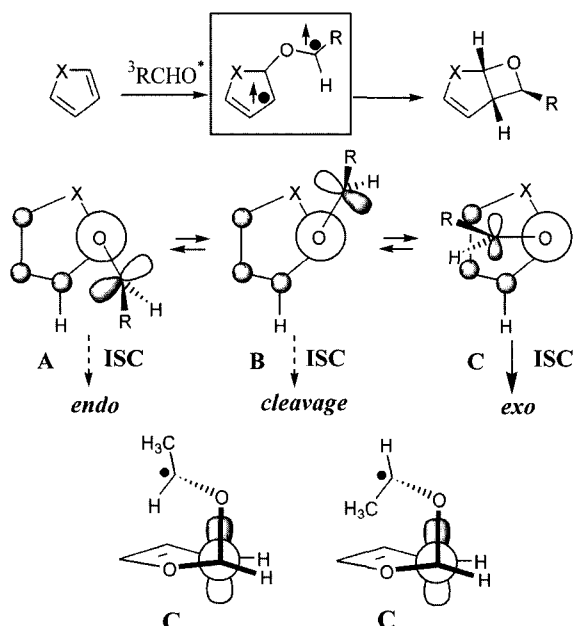
Scheme 13.

Scheme 14.

behaviour ? A simple conformational analysis which combines the three staggered triplet 1,4-biradical conformers **A,B** and **C** with the optimal geometries for maximum spin-orbit coupling is self-explanatory (Scheme 14).

As already described for the cycloalkene case, ISC from **A** and **C** are expected to lead to *endo-* and *exo*-diastereoisomers, respectively. Using density functional theory (DFT) we determined if structure **C(C')** with an orthogonal arrangement of the two spin-bearing orbitals corresponds to an energy minimum. As model reaction we used the 1,4-biradical from furan and triplet acetaldehyde. Structure **A** represents the global energy minimum (fully optimized), the restricted conformation **C** is 9.9 kJ/Mol higher in energy, separated by an activation barrier of 28 kJ/Mol. This activation energy is obviously too high due to the conformational restriction for rotation about the exocyclic O-C(H,Me) bond. The alternative arrangement **C'** with the methyl group pointing toward the ring plane is much higher in energy and should be less significant in this reaction. If structure **C** (and not **A**) represents the main contribution to product formation, a high *exo*-selectivity is expected due the nearly exclusive formation of the "methyl-up"

conformation **C**. The torque induced in conformer **C** rotates the large substituent (methyl or any other substituent) in opposite direction with respect to the ring plane and results in the formation of the major (*exo*) diastereoisomer.

What happens if the hydrogen in structure **C** is exchanged by a substituent larger than methyl, i.e. if ketones are used as triplet carbonyl substrates ? Following the arguments from above, both structures **C** and **C'** are no longer relevant and only structure **A** remains as the SOC-controlling arrangement for the ISC process. Thus, all triplet carbonyl substrates with substituents exceeding a limiting degree of steric interaction were expected to give *endo*-selective C-C bond formation. This model offers an explanation for the dichotomy that some carbonyl substrates (e.g. phenyl glyoxylates) give idential diastereoselectivity with cyclo-1,3-dienes <u>and</u> with the corresponding cycloalkenes, whereas other carbonyls (e.g. aldehydes or acetophenone) show a completely different selectivity pattern. An alternative explanation for the high *exo*-selectivity in furan-aldehyde photocycloadditions which we have suggested earlier, was the extended lifetime of the singlet 1,4-biradical which is formed after ISC. This concept, however, predicts thermodynamic control for the formation of <u>all</u> cycloaddition products, whether they are formed from triplet excited aldehydes or ketones, esters, etc. Obviously, this is not the case (see Scheme 15). Thus, an interaction between the allylic and the exocyclic radical in the 1,4-triplet biradical (as depicted in structures **C**) must be crucial for the dominance of this biradical geometry for rapid ISC. This effect can be described as a secondary orbital interaction which facilitates intersystem crossing by means of an increase in spin-orbit coupling.

Recently, we extended the photo-aldol route (furan/aldehyde photocycloaddition) [19] and developed the oxazole-based process to α-amino β-hydroxy ketones [20]. As substrate, the commercially available 2,4,5-trimethyloxazole (**19**) was used and the oxetanes **20** were formed from aldehydes with excellent (*exo-*)diastereoselectivities (Scheme 15).

Theoretical work

Since the seminal paper by Salem and Rowland on triplet biradical behaviour in solution [9], several important contributions on the nature of spin-orbit coupling elements for the control of the lifetime and the geometry of triplet biradicals have been published, mentioned already in the mechanistic discussion. Recently, conformational dependence of spin-orbit coupling (SOC) in flexible Paternò-Büchi (PB) diradicals has been studied with high-level *ab initio* methods by Kutateladze

Scheme 15.

C-C-O-C 30   C-C-O-C 110

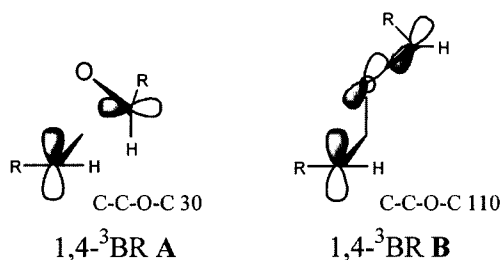$1,4\text{-}^3\text{BR A}$ $1,4\text{-}^3\text{BR B}$
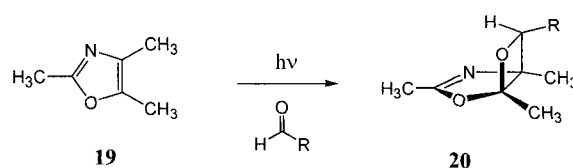
Figure 6.

for the originally published model system 2,3-dihydrofuran and benzaldehyde (semiempirical geometries) [21]. The *ab initio* results revealed two distinct areas of elevated SOC values (Figure 6), one corresponding to the region whereby a cisoid conformation in the C-C-O-C fragment brings the two odd-electron orbitals closer to each other (**A**), and the other area corresponding to the partially eclipsed conformation lacking direct overlap between the spin centers (**B**).

The largest singlet-triplet energy gap, approximately 2 kcal/mol, was found for a *gauche* conformer (also a minimum SOC conformation). This accounts for the experimental results, i.e. high diastereoselectivity and moderate quantum yields as well as relatively short biradical lifetimes in comparison with the tetramethylenes. The decisive role of the oxygen in the 2-oxatetramethylene radical becomes apparent in the second important SOC conformer **B** from which lower diastereoselectivity is expected. If this assumption is correct, improved non-induced diastereoelectivity is to be expected for the bond formation from triplet tetramethylene (*vide infra* for Norrish/Yang reactions).

Concentration and Temperature Studies

Essential for demonstrating different simple diastereoselectivities in singlet and triplet routes was the detection of the concentration dependence of the stereoselectivity of the Paternò-Büchi reaction [22]. We could show, that for carbonyl substrates which have reactive singlet and triplet states, every pair of carbonyl and alkene component exhibits one characteristic substrate concentration where a 1:1 ratio of singlet and triplet reactivity, i.e. spin selectivity, could be detected. The shape of these concentration/diastereoselectivity correlations reflects the different kinetic contributions to this complex reaction scenario (Scheme 16). Recognize that the difference to Scheme 1 is, that identical products are now formed *via* the singlet as well as the triplet path, only with different C/D-composition. The selectivity C/D is controlled by the geometry of the conical intersection for the singlet reaction [23] and by the optimal ISC-geometry of the 2-oxatetramethylene biradical (^{3}OTM) for the triplet reaction [5]. The concentration dependence for the propionaldehyde/2,3-dihydrofuran reaction is depicted in Figure 7.

At low concentrations (triplet conditions), the diastereoselectivity approaches a maximum *endo/exo* value of 85:15,
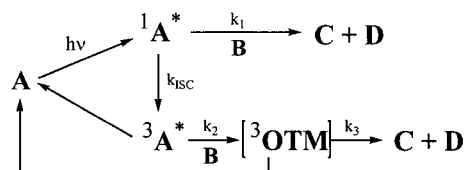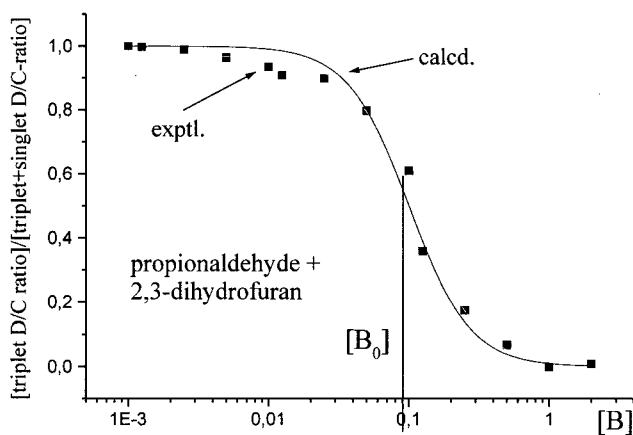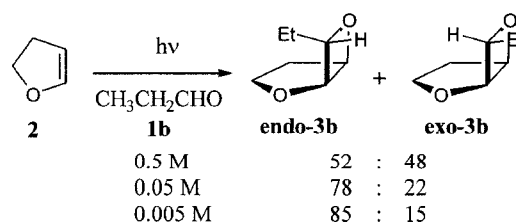

Scheme 16.

Figure 7. Concentration dependence of the diastereoselectivity of the Paternò-Büchi reaction of 2,3-dihydrofuran (2) with propionaldehyde (1b) at 293 K in benzene.

0.5 M	52	:	48
0.05 M	78	:	22
0.005 M	85	:	15

Scheme 17.

much higher than our original experiments indicated which were conducted at higher concentrations. Thus, the substituent effects on SOC-controlled intersystem crossing geometries were even more pronounced than originally expected! At high concentration (singlet conditions), the diastereoselectivity decreased to 52:48 (Scheme 17).

Concerning the temperature depencences, our initial assumption was that the activation parameters should strongly differ for these two processes and consequently characteristic non-linear behaviour might occur during temperature variation. Prior to these experiments solvent viscosity effects were studied in order to keep apart these influences from temperature effects. The photocycloaddition of benzaldehyde (**1a**) with 2,3-dihydrofuran (**2**) was investigated as a typical triplet reaction with concentration-independent diastereoselectivity. Variation of the solvent viscosity over a large effective range (η=0.3 to 1500 cp) resulted in a weak but significant increase in endo-selectivity from 82% to 91% (Figure 8) [24].

More pronounced effects were detected for the analogue reactions with aliphatic aldehydes propionaldehyde (**1b**),
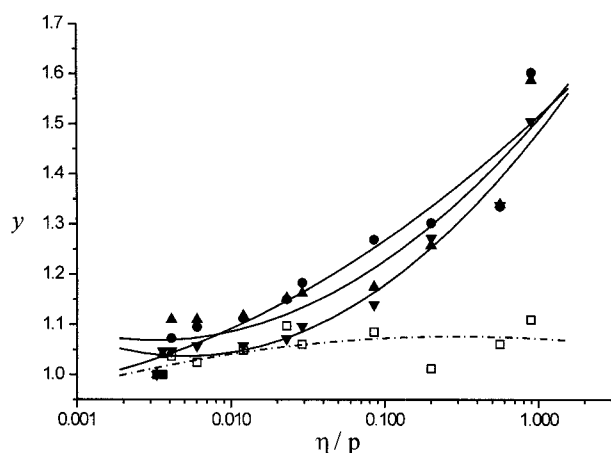
Figure 8. Viscosity dependence of the Paternò-Büchi reaction of 2,3-dihydrofuran (2) with aldehydes 1a-d (1a:_; 1b:_; 1c:_; 1d:_) at 293 K with y=endo/exo-diastereoselectivity normalized to 1.0 for the lowest solvent viscosity.

acetaldehyde (1c) and isobutyric aldehyde (1d) and dihydrofuran (2, 1 M substrate concentrations). In all cases, the diastereo-selectivity increased with increasing solvent viscosity. In the context of our mechanistic model (Scheme 16), an increase in solvent viscosity should favor the triplet channel due to a reduction in the diffusion rate limit (about 4 orders of magnitude in the experimental range).

In a next series of experiments, the temperature dependence of the endo/exo-selectivity was investigated at constant concentration (1 M). The aliphatic aldehydes RCHO 1b-d (R=Et, Me, iBu) gave characteristic non-linear curves with inversion points for 1c and 1d. The selectivity values given in Figure 9 are normalized with the starting points at 293 K (Figure 9).

The acetaldehyde (1c)/2 system shows the strongest deviation from linearity with an inversion temperature of -37°C. For this specific reaction, we have learned from concentration
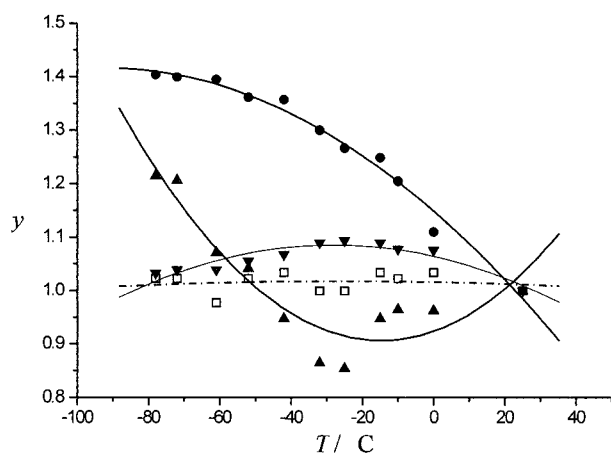

Figure 9. Temperature dependence of the Paternò-Büchi reaction of 2,3-dihydrofuran (2) with aldehydes 1a-d (1a:_; 1b:_; 1c:_; 1d:_) in n-hexane with y=endo/exo-diastereoselectivity normalized to 1.0 for 23°C.

studies that the acetaldehyde triplet adds to 2,3-dihydrofuran with high endo-selectivity (up to 85%) whereas the singlet gives the same products in moderate exo-selectivity (up to 65%). Thus, the temperature correlation can be interpreted qualitatively as follows: At room temperature under high concentration conditions, the cycloadducts 3c were formed with low exo-selectivity predominantely via the singlet-channel. This selectivity increases with decreasing temperature (as intuitively expected) and reaches an inversion point at -37°C. At this point, the triplet reactivity gains as much influence as necessary to turn around the selectivity direction. With further increasing temperature, the endo-selectivity becomes more and more dominant. The rate of the intersystem-crossing process (k_{ISC}) is expected to be nearly temperature-independent. This selectivity reversal could be detected for the 1c/2 system in a temperature region which is experimentally accessible. A marginal change in activation parameter, however, catapults this effect out of the experimental window (+40 to -78°C). This might have been the reason why we did not see an inversion effect in the propionaldehyde photocycloaddition. If this assumption is true, a change in substrate concentration might shift the inversion region back into the experimentally accessible range. Thus, we measured the temperature dependence of the 1b/2 system at 5 M (both substrates) and in fact detected an inversion point at -27°C. Presumably, in this case, the concentration increase led to a high-temperature shift of the inversion region. A reverse behaviour might exist for reactions with their inversion points at high temperatures which could be shifted to lower temperature with concentration variation. Yet, this effect could not be verfied experimentally.

The Norrish-Yang Photocyclization

The Yang reaction is defined as the photochemical formation of cyclobutanols from acyclic or cyclic carbonyl compounds initiated by an intramolecular γ-hydrogen abstraction (Norrish type II reaction) [25]. Acyclic carbonyl substrates often tend to cleave when electronically excited: beside the α-cleavage (Norrish I), β-cleavage often follows the formation of a 1,4-biradical of the 1-hydroxytetramethylene type. Thus, the Yang reaction is limited to those cases where the formation of a new carbon-carbon bond can efficiently compete with the cleavage of the α,β-bond. Due to the experimentally established fact that the first step of this reaction sequence (i.e. the transfer of a hydrogen atom) is reversible, the cleavage process, however, is not, special prerequisites are necessary for high-yielding Yang reactions. The selectivity-determining factors of the Yang cyclization reaction can be described using the three selection stages A-C which are depicted in Scheme 18.

After electronic excitation and intersystem crossing of the carbonyl compound, a chair-like conformation initiates the Norrish type II hydrogen transfer process (A). The primarily formed structure is that of a skew 1,4-triplet biradical. Biradical dynamics subsequently equilibrate syn- and anti-conformers (B) which have different intrinsic ISC-rates (vide supra) and
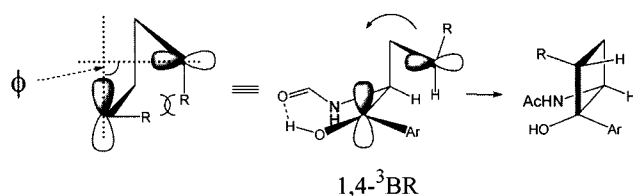
Scheme 18.

Scheme 19.

$1,4\text{-}^3\mathrm{BR}$
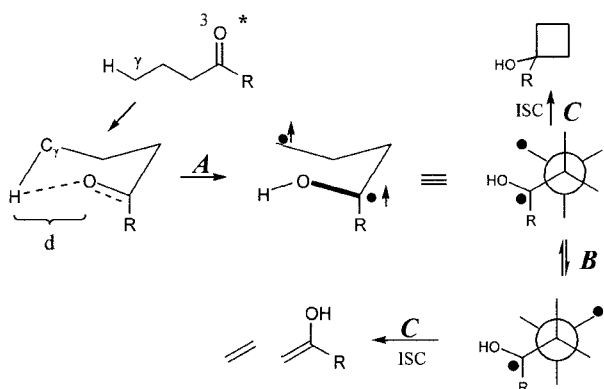
Scheme 20.

subsequently result in the formation of cyclization and cleavage products, respectively (**C**). The geometrical prerequisites for step **A** have been extensively investigated by Scheffer and coworkers for liquid- and especially solid-phase photolyses [26]. Following the classical assumption of an interaction between the reactive CH-bond and the p_y-orbital at the carbonyl oxygen, α-substituents can adopt a pseudoequatorial position. Following the crystal structure - solid state reactivity method, Scheffer have determined the distance and angular requirements for photochemical γ-hydrogen transfer. The optimal C=O⋯ H_γ distance d is close to the sum of the van der Waals radii of H and O (2.72 Å), the optimal ω-angle (describing the angle by which the γ-hydrogen atom lies outside the mean plane of the carbonyl group) is 52±5°, the optimal Δ-angle (describing the C=O⋯H angle) is 83±4°, and the optimal θ-angle (describing the C_γ-H⋯O angle) is 115±2°. These values have been extracted from a series of carbonyl substrates which have been analyzed in solid state and in fluid phase. The electronically excited carbonyl substrate has to pass through a chair-like transition state in order to achieve an efficient γ-hydrogen transfer. Norrish type I reactions always accompany this reaction and because of less restricted geometrical prerequisites often dominates. Concerning the nature of the activated CH-bond, a 1:30:200 selectivity for primary:secondary:tertiary CH is characteristic [3].

Our interest in this process originates from current work on photochemical amino acid transformations. In order to generate C-activated derivatives, α-amino acids were converted into N-acylated aromatic ketones. The photochemistry of these substrates **21** allowed the detailed analysis of processes **B** and **C** with respect to the stereoselectivity of the Yang-cyclization [27]. In all reactions, 2-acetylamino p-methyl-acetophenone, resulting from the Norrish type II cleavage reaction, was formed to different extents (beside ca. 10-20% of α-cleavage products). Both the *tert.*-leucine-derived substrate **21d** and the leucine-derived substrate **21b** gave solely the *cis*-diastereo-isomeric cyclobutanes **22d** and **22b**. The cyclization to cleavage ratios (CCR) were also similar: 63:37 and 58:42, respectively (Scheme 19). The product stereochemistry requires a high
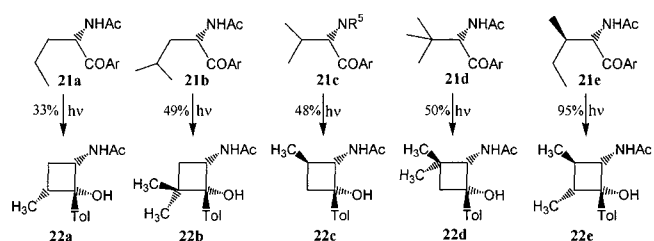
1,2-asymmetric induction which is convincingly explained by assuming a hydrogen bond formed already at the triplet biradical stage (Scheme 20).

The lifetimes of 1-hydroxytetramethylenes reported in the literature are in the 50 ns region and thus long enough to guarantee conformational flexibility at room temperature [8]. Hydrogen bonds stabilized Norrish II biradicals have been discussed several times based on experimental data and theoretical calculations. Calculations also resulted in the biradical $^3\mathbf{BR'}$ as global minimum. Additionally, this *syn*-biradical is in equilibrium with the *anti*-conformer by rotation about the C2-C3 bond. The equilibrium constant together with the hydrogen back transfer efficiency (from the *syn* structure) and the orbital orientation (p,p relative to the central C-C single bond) control the cyclization/cleavage ratio. The assumption is widely accepted that, after intersystem crossing, the singlet biradicals maintain conformational memory of their triplet precursors [28], i.e. the *anti* 1,4-biradical conformer gives exclusively cleavage products whereas the *syn* 1,4-biradicals can cleave and cyclize (Scheme 21). For $^3\mathbf{BR'}$ this means that process **C** is responsible for the CCR as well as for the stereoselectivity of the formation of new stereogenic centers (*vide infra*).

The latter aspect is not relevant for substrates **21b** and **21d** where the 1,2-asymmetric induction is dictated by the hydrogen bond and no further stereogenic centers are created. A second stereogenic center is created during the photolysis of the valine-derived substrate **21c** (Scheme 22).

The calculation (PM3) for the *syn*-biradical $^3\mathbf{BR'_c}$ resulted
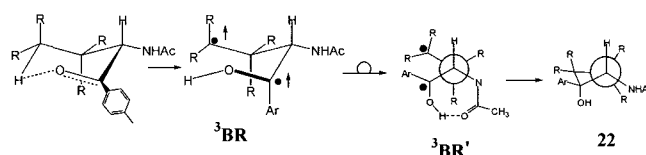
Scheme 21.
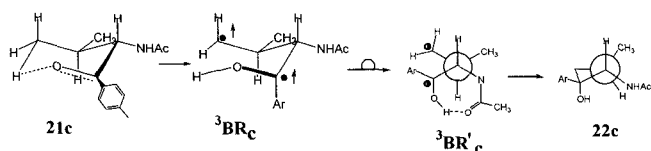
Scheme 22.

in a global minimum conformation with a strong hydrogen bond (C=O···HO: 1.80 Å, C(sp_2)-C(sp_2): 2.91 Å). In ^{3}BR$'_c$ two *gauche* interactions exist whereas in the alternative structure ^{3}BR$''_c$ three *gauche* interactions destabilize the conformer. The latter intermediate is expected to isomerize into its *anti* isomer, which subsequently undergoes cleavage. Another mechanistic alternative is the assumption of a highly stereoselective hydrogen abstraction from only one of the two diastereotopic methyl groups. On this stage of our research we could not distinguish between these two alternatives. As described already in detail, spin-orbit coupling (SOC) controlled geometries are preceding product formation. Calculations resulted in large SOC values for *syn* geometries and lower values for *anti* geometries [12]. Assuming that in the *syn*-conformer the hydroxy group localized at the benzylic radical is sterically more demanding, the SOC-principle (Scheme 20) predicts the correct relative product stereochemistry for C3-C4 (*cis* configuration with respect to methyl and hydroxy).

Summarizing the experimental results and the proposed reaction model, a three-stage selection protocol results which enables the prediction of the correct chemo- and stereoselectivity. The hydrogen abstraction (step **A**) differentiates between diasterotopic hydrogens due to the strict geometrical prerequisities, biradical dynamics (step **B**, i.e. rotation about C1-C2 and C2-C3) control the 1,2-asymmetric induction as well as the cyclization/cleavage ratio. Eventually, SOC-controlled ISC (step **C**) directly leads to the formation of the final C-C bond and thus determines the stereochemistry of the conversion of the two radical centers into new stereogenic centers.

SUMMARY AND CONCLUSIONS

We are able now to predict the effect of substituents, concentration, pressure and temperature changes as well as solvent properties on the stereoselectivity of photoinduced reactions involving triplet biradicals on the basis of the spin-orbit coupling (SOC) geometry model. By determining the spin-selectivity of a given photochemical reaction, the specific geometries for triplet to singlet intersystem crossing at the stage of the triplet biradical PES can be deduced. By variation of solvent polarity, competing photoinduced electron transfer reactions can be detected. Further studies are on the way in order to differentiate between concerted singlet photocycloaddition, triplet photocycloaddition controlled by SOC or hyperfine coupling (HFC), respectively, and photoinduced electron transfer (PET).

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