Selectivity Control in Electron Spin Inversion Processes: Regio- and Stereochemistry of Paternò—Büchi Photocycloadditions as a Powerful Tool for Mapping Intersystem Crossing Processes

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ABSTRACT

Regio- and stereoselectivity in ene-carbonyl photocycloadditions depend on the spin multiplicity of the excited carbonyl state, although both singlet and triplet states produce the cycloadducts with comparable chemoselectivity. The correlation between selectivity and spin state was evaluated by concentration, temperature, and solvent viscosity studies. The higher selectivity observed for triplet reactions is rationalized by the optimal conformations of the intermediate 2-oxabutane-1,4-diyls for intersystem crossing (ISC) to the singlet manifold, controlled preferentially by spin—orbit coupling. This weak interaction connected with ISC can lead to substantial control of regio- and stereoselectivity. The role of hyperfine coupling is demonstrated by magnetic isotope effects.

Introduction

In a classical organic reaction involving (closed-shell) ground states of reactants and products, the electron spin is a negligible quantity, influencing neither the efficiency nor the selectivity of a transformation. The number of exceptions is, however, constantly increasing and calls the former general statement into question. The best known historical exceptions from this general statement in organic synthesis are carbene cycloadditions (singlet versus triplet reactivity) and the pronounced reactivity difference between ground-state triplet and the first excited singlet state of oxygen. Whenever metals with different oxidation states come into the game, changes between different spin states are known to accompany the progress of the reaction and can modify a reaction from a process without change in spin state to a situation where the spin change completely determines the rate and selectivity. This latter phenomenon has been termed two-state reactivity (TSR) by Schwarz and Shaik[1] and is a new concept for describing chemical reactivity in the context with interspin crossing.[2]

In organic photochemistry, different spin states are involved by nature of the excited states, which are often different from their ground-state precursors as well as closed-shell products.[3] A plentiful number of reactions are known that are initiated by triplet excited molecules in

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Scheme 1. Reaction Scheme for Spin-Selective Processes—Paternò–Büchi Model Reaction
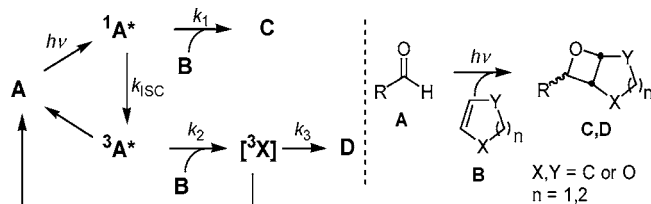
carbonyl, enone, alkene, or arene photochemistry.[4] Traditional mechanistic analyses of photochemical reactions involving triplet excited substrates have partly ignored the spin state problem and focused on the primary interactions on the triplet surface (i.e., as single-state reactivity {SSR} approach). The formation of closed-shell products, however, in all cases requires spin inversion (intersystem crossing, ISC) and with that, reactivity and selectivity of the global reaction is spin-related. The term *spin chemistry* was created in this context.[5] The key feature of all processes in context with spin chemistry phenomena is the Wigner spin conservation rule.[6] With other words, 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, is transformed into real world because this rule is *not* strictly observed and mechanisms exist that allow spin flips coupled with chemical reactions. This opens an avenue for new effects on the efficiency and selectivity of reactions, for example, magnetic field or magnetic isotope effects.[7] An extremely fruitful field of spin-sensitive processes are photochemical reactions initiated by triplet excited carbonyl compounds.

The reaction that we have studied in the recent decade is an archetype carbonyl reaction: the Paternò–Büchi photocycloaddition of an electron-rich alkene with a prochiral electronically excited carbonyl component (aldehyde or α-ketoester).[8] The advantage of this reaction with respect to spin chemistry is that both the first excited singlet state and the corresponding triplet state of the carbonyl component are active substrates for the Paternò–Büchi process, that is, both deliver oxetanes as major products (identical *chemoselectivity*). The spin profile thus detected for this reaction is shown in Scheme 1 with **C** and **D** representing different *regio-* or *stereoisomer* compositions. The 2-oxatetramethylene biradicals are clearly established reactive intermediates ([3]**X** in Scheme 1) from the triplet surface with lifetimes in the nanosecond region.[9] From a recent multiconfiguration self-consistent field (MC-SCF) study of the singlet and triplet Paternò–Büchi reactions,[10] it was predicted that ISC from triplet to singlet will lead to the same biradical ground-state pathways that can be entered via singlet photochemistry. Our experimental studies on the concentration, temperature, solvent viscosity, and solvent polarity dependence of the Paternò–Büchi reaction revealed, however, that there are distinct *spin-selectivity* effects. In this Account, we present our recent analyses on the origin of the regio- and stereoselectivity in the Paternò–Büchi reaction of

cyclic vinyl ethers with carbonyl compounds. The experimental and computational investigations do unambiguously show that spin-state (singlet versus triplet) of the excited substrate, the structure of the intermediate 1,4-biradicals [3]**X**, and the preferred conformation for accelerating the ISC process in the triplet biradicals determine the regio- and stereoselectivities of the closed-shell product oxetanes.

Mapping Singlet and Triplet Selectivities in Paternò–Büchi Reactions

To evaluate the differences in diastereoselectivity in the singlet and triplet channel, we studied the concentration dependence of this feature. As obvious from Scheme 1, following direct excitation, the triplet excited states [3]**A*** are formed subsequently in a unimolecular process (k_{isc} ranging from 10^9 to 10^{12} s^{-1}), and by increasing the amount of trapping reagent **B**, the singlet selectivity can be differentiated from the triplet selectivity. Some results of this simple approach, which is also often used in photochemistry to determine excited state lifetimes and ISC rates, are shown in Figure 1. Due to the rapid ISC rate of aromatic aldehydes, the benzaldehyde photocycloaddition occurs solely from the triplet excited state and shows no
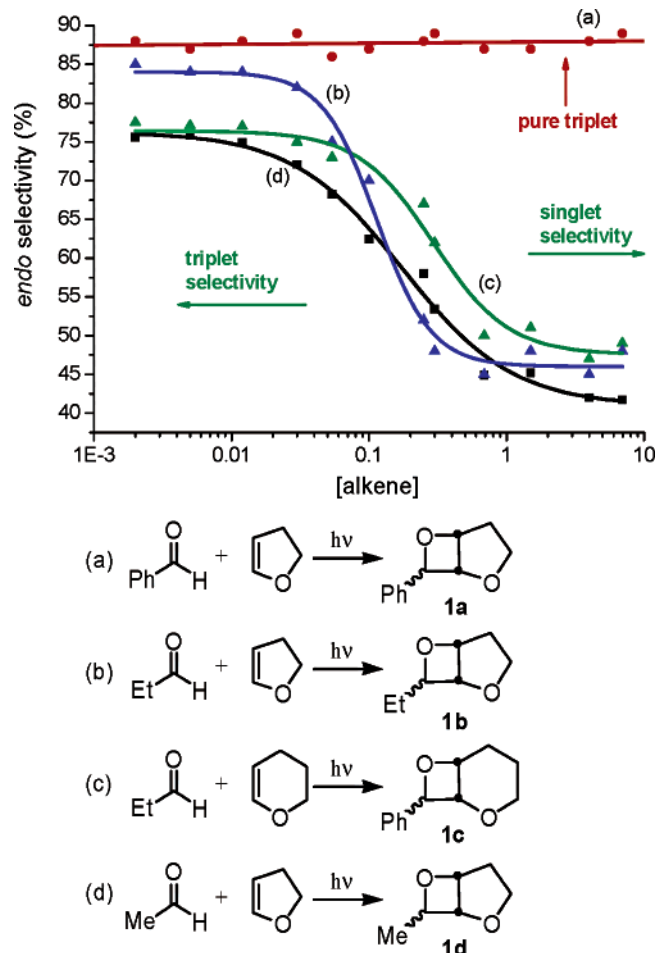

FIGURE 1. Concentration–endo selectivity profiles: (a) red circles, benzaldehyde/dihydrofuran; (b) blue triangles, propionaldehyde/dihydrofuran; (c) green triangles, propionaldehyde/dihydropyran; (d) blue squares, acetaldehyde/dihydrofuran.
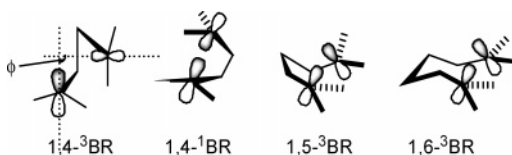
FIGURE 2. Structures of 1,*n*-biradicals with optimal spin–orbit coupling geometries.

concentration dependence of the high endo selectivity (Figure 1a). Aliphatic aldehydes with singlet excited state lifetimes in the nanosecond time scale did clearly show surprising concentration dependences: in the high-concentration region (mapping singlet reactivity), low diastereoselectivities were detected for all combinations of aldehydes and alkenes; in the low-concentration region (mapping triplet reactivity), the selectivities raised to much higher values (Figure 1b–d). In all cases, the thermodynamically disfavored endo diastereoisomers **1a–d** were formed preferentially from the triplet potential energy surface. We rationalized this unusual effect by assuming specific triplet biradical geometries that are prone to rapid ISC to the singlet manifold due to optimal spin–orbit coupling.[11] Thus, these weak interactions (SOC constants are only some calories per mole for 2-oxatetramethylene biradicals) lead to a pronounced diastereodifferentiation (in the kilocalorie per mole region).

From the sigmoidal concentration/selectivity correlations, characteristic concentration values were determined for which the contributions of singlet and triplet excited states to product formation are equal, resulting in isospin selectivities.[12] By this approach, the spin profile of the two lowest excited states of the carbonyl group can be evaluated without selective excited-state generation (either by triplet sensitization or by addition of triplet quenchers). For a multitude of examples including also acyclic alkenes as substrates,[13] this spin-dependent stereoselectivity was observed and, for the majority of the examples, *contra*-thermodynamic stereocontrol. The initial rationale for this counterintuitive result (spin-barrier free singlet reactions result in low selectivity and spin-barrier linked triplet reactions result in high selectivity) was that in the short-chain triplet 1,4-biradicals specific spin–orbit coupling (SOC) phenomena determine the geometries of triplet biradical intermediates when crossing into the singlet potential hypersurface. Spin–orbit coupling is largely accepted as the dominant factor for triplet biradicals connected by short hydrocarbon chains as in tetramethylenes or in 2-oxatetramethylenes, and geometrical factors strongly influence SOC.[14] Recent ab initio calculations have revealed earlier predictions of a pronounced SOC dependence on the spatial orientation of the spin-bearing carbon atoms (ϕ angle) in 2-oxatetramethylenes.[15] A set of 1,*n*-biradical structures can be simulated ($n = 4,5,6$) either for triplet or singlet multiplicity (Figure 2) with optimal orbital alignment facilitating ISC (induced by spin–orbit coupling) or direct bond formation (in case of the singlet biradical 1,4-^{1}BR). If the structure of singlet biradicals generated from singlet excited carbonyl compounds is similar to the geometry derived from the triplet biradical 1,4-^{3}BR after ISC, identical product diastereose-

lectivities are expected. However, as mentioned in Figure 1, the diastereoselectivity is largely dependent on the concentration of alkenes, and thus, conformational memory (a term initially used by Scaiano in this context)[16] is depicted in the triplet photocycloaddition channel.

Solvent Viscosity and Polarity Effects: The Borderline of Biradical and Photoinduced Electron Transfer (PET) Reactivity.

In the multistep scenario depicted in Scheme 1, the solvent interacts in a 2-fold manner: solvent polarity influences the reaction mode, that is, induces a switch from homolytic to electron-transfer reactivity; solvent viscosity influences the spin selectivity by changing the bimolecular diffusion-limited rate constant. In Figure 3
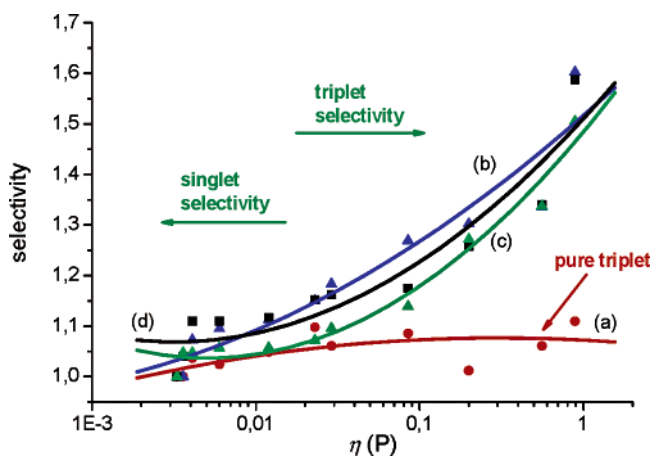

FIGURE 3. Viscosity–selectivity (endo/exo diastereoselectivity normalized to 1.0 for the lowest solvent viscosity) profiles: (a) red circles, benzaldehyde/dihydrofuran; (b) blue triangles, propionaldehyde/dihydrofuran; (c) green triangles, propionaldehyde/dihydropyran; (d) blue squares, acetaldehyde/dihydrofuran, all at 1.0 M concentrations.

is shown the effect of solvent viscosity on the diastereoselectivity of the photocycloaddition of the same substrate pairs used for the concentration series. At solvents with high viscosity, the diastereoselectivity had increased due to exclusive singlet contribution. Concurrently, the relative yields for these oxetanes decreased and new products appeared, which can be ascribed to an electron-transfer process.[17]

In the case of the benzaldehyde/dihydrofuran pair, the characteristic PET products were the isomeric oxetanes *endo-* and *exo-***1a′** (Scheme 2). This switch in regiochemistry (vide infra for a substrate trick to completely invert the regioselectivity) is accompanied by an inversion of diastereoselectivity,[18] from high endo selectivity for **1a** to high exo selectivity for **1a′**. In benzene solution, no PET-characteristic products **1a′** were found, whereas in acetonitrile 22% of **1a′** were formed besides radical coupling products and the non-PET addition products **1a**.

The diastereomeric ratio for **1a′** represents approximately thermodynamic control and relates to the combination of a singlet precursor species, either the 1,4-singlet biradical pre-*exo*-1,4-^{1}BR (from the radical ion pair

Scheme 2. Regioselectivity and Diastereoselectivity as Indicators for Biradical versus Photoinduced Electron Transfer (PET) Processes in Paternò–Büchi Reactions

Scheme 4. Exclusive Formation of *exo*-Oxetane in the PB Reaction of Furan
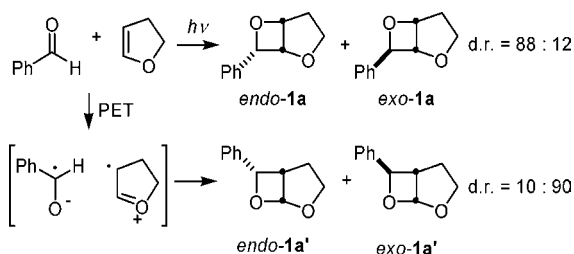
by charge recombination) or a 1,4-zwitterion. In any case, the diastereoselectivity reflects the orbital orientation most suitable for *spin-unrestricted* C–C bond formation, whereas the diastereoselectivity in the triplet photocycloaddition (leading to **1a**) indicates the phenomena of spin-restriction and a conformational memory expressed by the specific *spin stereochemistry* (Figure 4).
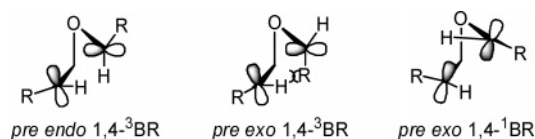

FIGURE 4. Orbital and substituent orientation in strongly interacting biradical conformers.

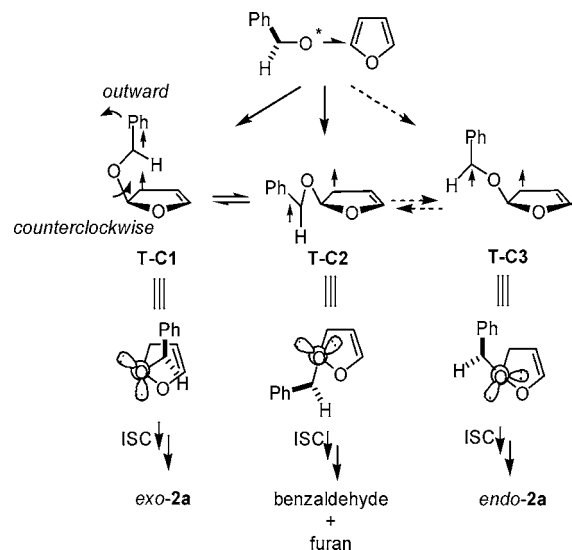# The Total Switch in Regio- and Stereoselectivity in Heteroaromatic Substrates

As mentioned above for the regio- and stereoselectivity in the reaction of 2,3-dihydrofuran with benzaldehyde, *endo*-3-alkoxyoxetane **1a** was formed as a major isomer.[19] In sharp contrast, exclusive formation of *exo*-2-alkoxyoxetane **2a** was reported in the reaction of furan (Scheme 3).[20] The regio- and stereoselectivity were also observed

Scheme 3. Total Switch in Regio- and Stereoselectivity in the Paternò–Büchi Reaction of Benzaldehyde with Dihydrofuran and Furan, Respectively
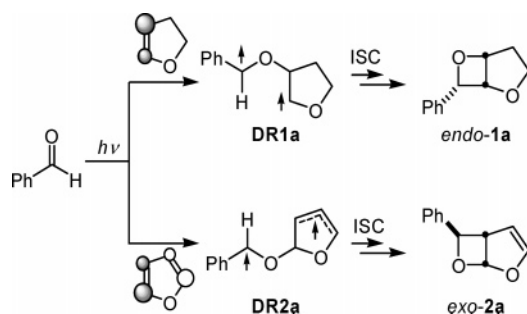
in other heteroaromatic substrates (e.g., oxazoles).[21] The dramatic difference of the regioselectivity (2-alkoxyoxetane versus 3-alkoxyoxetane) can be convincingly explained by (i) the character of nπ* excited carbonyl group and (ii) the radical stability of the intermediate triplet 2-oxabutane-1,4-diyls. As suggested by Hammond, Turro and co-workers,[22] the excited state of carbonyl compounds has an electrophilic radical character on the oxygen atom. Thus, the half-filled n-orbital of the oxygen is expected to attack alkenes preferably at the site of higher frontier

electron density. As can be easily imagined from the HOMO coefficients of the cyclic alkenes (Scheme 3), the oxygen should attack the 3-position of dihydrofuran to generate the intermediate triplet biradical **DR1a**. In contrast, the biradical **DR2a** is expected to be selectively formed by the attack by the oxygen at the 2-position of furan. The triplet biradical **DR2a** is more stable than the regioisomer derived from the attack by the oxygen at the 3-position of furan, since the unpaired electron on the furan ring in **DR2a** is stabilized by allylic conjugation. Thus, the exclusive formation of 2-alkoxyoxetane is the energetically favored process in the reaction of furan derivatives.

As pointed out in the endo-selective formation of 3-alkoxyoxetanes **1**, the conformational distribution of intermediate triplet biradicals and the bond rotations enhancing triplet → singlet ISC processes play a crucial role to determine the stereochemical outcome. UDFT calculations at UB3LYP/6-31G* level of theory uncovered the equilibrium structures in **DR2a** (Scheme 4).[23] The plane of the benzyl-radical part in the optimized structures is perpendicularly located to the furan ring. The conformational preference is explained by the energetic stabilization caused by the orbital interaction between the 2p AO of the oxygen atom and the p-orbital of the benzyl radical. It should be noted that among the possible conformers **T–C1–C3** the outside-gauche structure **T–C3** does not exist as a real minimum. The conformational distribution is quite different from that in **DR1a**. In **DR1a**, the outside-gauche conformer was reported to be the energy minimum structure (Figure 4) that is the precursor of *endo*-oxetane.[15] The energetic preference of **C1** and **C2** in **DR2** is rationalized by stereoelectronic effect,[24] that is, gauche effect, in the ketal functionality. Thus, the orbital overlap of the n orbital of oxygen with the σ* orbital of the C–O bond in the furan ring is quite effective in **C1** and **C2**. However, the orbital overlap is poor in the conformer **C3**. The outside-anti conformer **C2** is nonproductive to go back to the starting compounds after the

ISC process to the singlet state. The inside-gauche conformer **C1** affords the *exo*-oxetane **2a** by *counterclockwise* rotation of the primarily formed C–O bond and concomitant *outward* rotation of the phenyl ring. The "productive" bond rotations are proposed to enhance the ISC process due to the increase of the SOC value, since these motions decrease the distance of the two radical sites.[11,15] The structure of the intermediate triplet biradical properly rationalizes the stereochemical result in the Paternò–Büchi reaction of furan.

Spin-State Effect on Regioselectivity (Double-Bond Selection) in Unsymmetrically Substituted Furans

There were scattered reports on the regioselectivity (double-bond selection, **2** versus **2′**) in the Paternò–Büchi (PB) reaction of unsymmetrically substituted furans (Scheme 5). Benzaldehyde photochemically adds to the double-

Scheme 5. Regioselectivity (Double-Bond Selection) of Unsymmetrically Substituted Furans
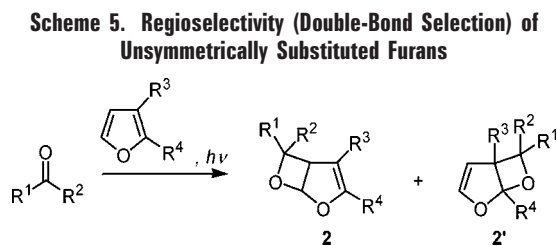
bonds of 2-methylfuran to afford a 1:1 mixture of oxetanes **2** and **2′**.[25] In contrast, the selective formation of oxetane **2** or **2′** was reported in the PB reaction of 2-silylfuran[26] or 2-acetylfuran[27] with aromatic aldehydes. In the photoreaction with benzophenone, Rivas[28] found the selective formation of higher substituted oxetanes **2′** both in the reactions of 2-methyl- and 3-methylfuran at ambient temperature. The rule of maximum radical stability in intermediate triplet biradicals[29] does not account for the regioselectivity observed in the Paternò–Büchi reactions. Our systematic investigations[23,30] on regioselectivity provided the convincing evidence regarding the mechanism, which has been debated until now.

As mentioned above in the concentration effect on stereoselectivity in cyclic monoalkenes,[12] the spin state (singlet versus triplet) in the excited state of carbonyl compounds plays a crucial role to determine the stereochemical outcome. The notable spin-state effect was also observed in regioselectivity for the PB reaction of unsymmetrically substituted furan with acetone at ambient temperature (Scheme 6).[30] Thus, in contrast to the selective formation of higher substituted oxetane at lower concentration of 2-siloxyfuran (0.01 M), the two isomeric oxetanes were observed under the conditions of higher concentration of the furan (0.2 M). The results clearly suggest that the high regioselectivity (>80% de) arises from the *triplet* state of acetone (under low concentration of the furan), while the singlet excited state of acetone regiorandomly produces the two isomeric oxetanes. The notable spin-state effect on the regioselectivity suggests that the intermediate triplet biradicals and the step of their

Scheme 6. Spin-State Dependence of Regioselectivity (Double-Bond Selection)
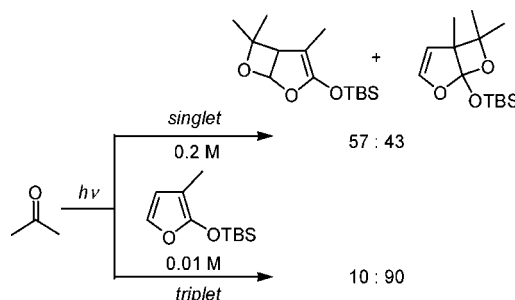
ISC process to singlet states play an important role to determine the inherent selectivity. As mentioned below, spectroscopic and computational investigations support the intervention of triplet biradicals and the importance of their conformational distributions in regioselectivity (double-bond selection).

Temperature Effects on Triplet Photocycloadditions

Regioselectivity (double-bond selection) depends not only on the spin state of excited carbonyl compounds but also on reaction temperature. Typical temperature dependence of regioselectivity (double-bond selection) is shown in Scheme 7 and Figure 5 for the Paternò–Büchi reaction of methyl-substituted furans with benzophenone. In the reaction of 2-methylfuran (reaction a), the regioselectivity **2a/2a′** *nonlinearly decreased* from 42/58 to 19/81 with
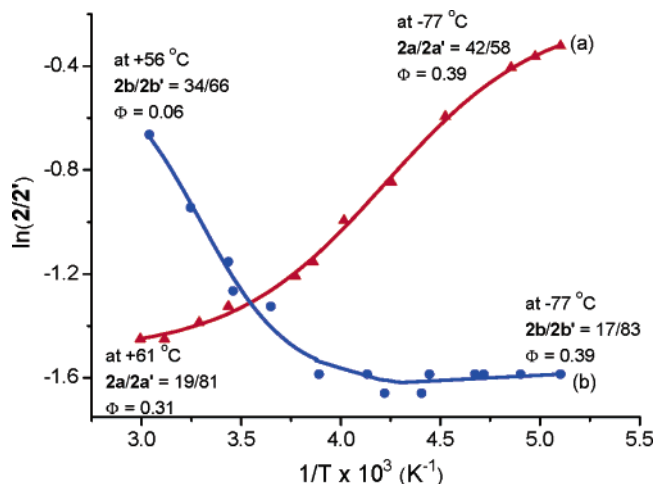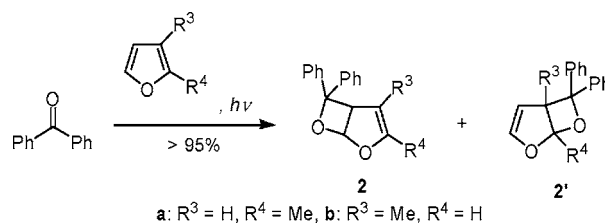

**FIGURE 5.** Eyring plots of regioselectivity, $\ln(2/2')$, against $1/T$ (K^{-1}) in the Paternò–Büchi reaction of (a) red triangles, 2-methylfuran (**2a**) and (b) blue circles, 3-methylfuran (**2b**) with benzophenone.

**Scheme 7. Spin-State Dependence of Regioselectivity (Double-Bond Selection)**

a: R^3 = H, R^4 = Me, b: R^3 = Me, R^4 = H

Scheme 8. Regioselectivity (Double-Bond Selection) in the Paternò–Büchi Reaction of Methyl-Substituted Furans with Benzophenone

Scheme 9. Substituent Effects on the Equilibrium Constants K and K'
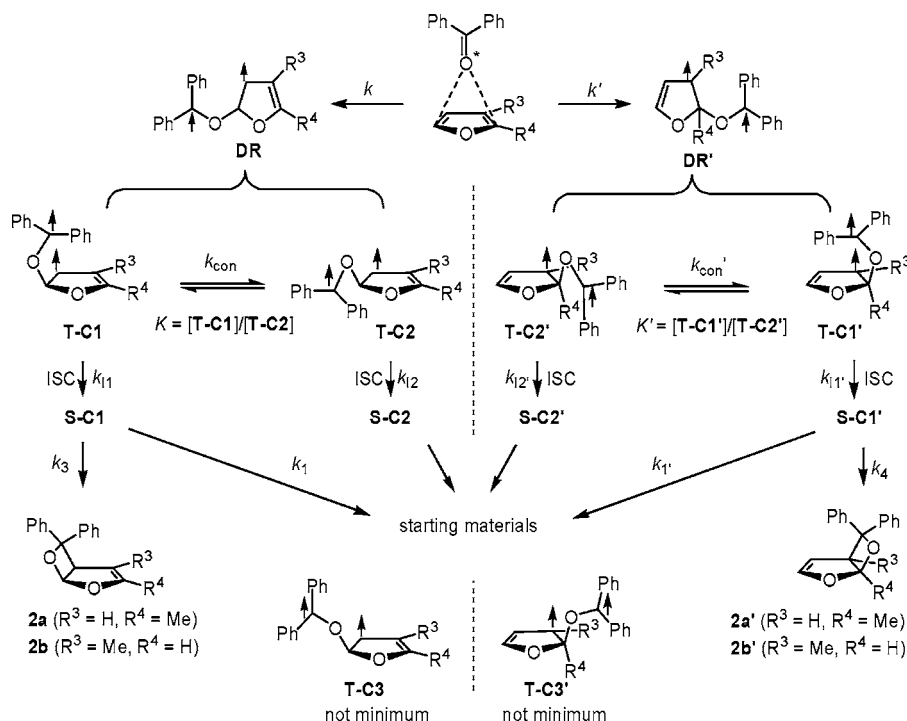
increasing the reaction temperature (Figure 5a). In contrast, in the reaction of 3-methylfuran (reaction b), the formation of the lower-substituted oxetane **2b** *nonlinearly increased* with increasing the temperature, **2b**/**2b**′ = 17/83 at −77 °C and 34/66 at +56 °C (Figure 1b). It should be noted that the quantum yields (Φ) for the formation of oxetanes **2** and **2**′ were also temperature-dependent. Thus, the yields decreased with increasing temperature (Figure 5). The dramatic decrease of the quantum yield was observed for the reaction of **2b**, Φ = 0.39 at −77 °C and 0.06 at +61 °C (Figure 1b). How can we understand the unusual temperature effect on both the regioselectivity and quantum yield observed in the pure triplet-state photoreactions?

The nonlinear Eyring plots clearly suggest that oxetanes **2** and **2**′ are formed in the reaction of two steps or more. Indeed, we observed the intermediate triplet biradicals **DR** and **DR**′ (λ_{max} = ca. 530 nm, τ = 3−5 ns at 25 °C in acetonitrile) by transient absorption spectroscopic analyses on the picosecond time scale (Scheme 8). If only the double-bond selection (k/k') by triplet benzophenone controls the regioselectivity (**2**/**2**′), the Eyring plots should be linear. Thus, the regioselectivity is not always determined by the first selection in the double bonds. Computational studies on the triplet biradicals clarified that among the possible conformers the inside-gauche and outside-anti conformers, **T−C1**, **T−C2**, **T−C1**′, and **T−C2**′, are located as energy minimum structures.[23] Outside-gauche conformers **T−C3** and **T−C3**′ were, however, calculated not to be the equilibrium geometries. The conformational preference can be reasonably explained by the gauche effect in the ketal functionality (vide supra). The energy barriers ($\Delta E^{\ddagger}$ = ca. 5−8 kcal/mol) between the conformers and equilibrium constants (K and K') were obtained by the potential energy surface analyses. It
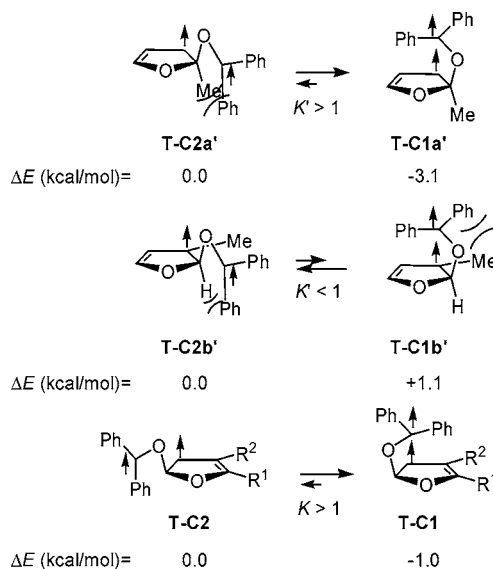
should be noted that the equilibrium constants (K') in biradicals **DR**′ are largely dependent on the position of methyl group in the furan ring, although the position of the substituent does not affect the equilibrium constants K in biradicals **DR** (Scheme 9). The small substituent effect on the equilibrium constants K is due to the enlarged distance between the substituents R[3],R[4] and the diphenylmethyl radical moiety. Thus, the productive conformer **T−C1a**′ is calculated to be more stable than the nonproductive conformer **T−C2a**′ ($K' > 1$). In contrast, the productive conformer **T−C1b**′ is less stable than the nonproductive conformer **T−C2b**′ ($K' < 1$). How do the relatively large rotational barriers and the substituent
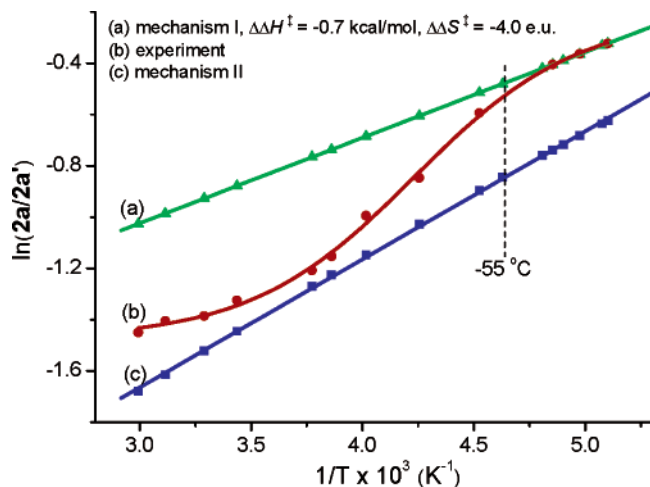
FIGURE 6. Theoretical and experimental Eyring plots in the Paternò–Büchi reaction of benzophenone with 2-methylfuran.
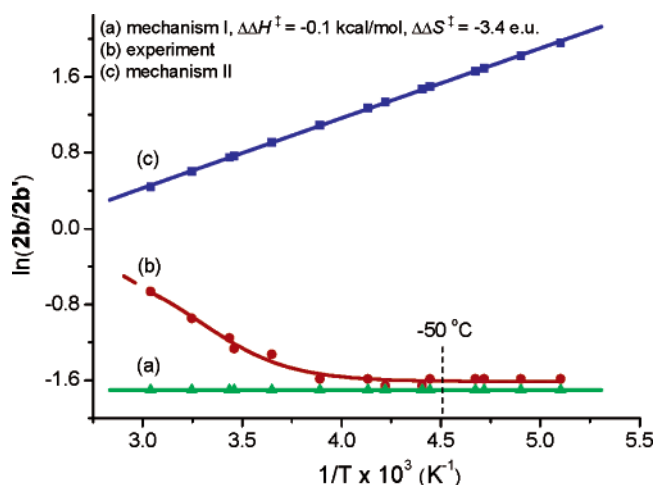

FIGURE 7. Theoretical and experimental Eyring plots in the Paternò–Büchi reaction of benzophenone with 3-methylfuran.

effect on the equilibrium constants affect the regioselectivity in the PB reactions?

Near-zero activation energies provide strong evidence that the rate constant of the ISC process is temperature-independent,[16] while the rate constant of conformational changes is temperature-sensitive due to the existence of an energy barrier. On the basis of the generally accepted temperature effect on ISC process and conformational changes, a mechanism shown in Scheme 8 is proposed for interpreting the nonlinear temperature effect and the substituent effect on the regioselectivity. At low temperature, the ISC process is faster than the conformational changes ($k_I > k_{con}$, mechanism I), and thus the regioselectivity (**2/2′**) is expected to be determined by the initial double-bond selection ($k/k′$, green lines in Figures 6 and 7).[23] When the conformational changes overcome the ISC process ($k_I < k_{con}$, mechanism II) at higher temperatures, the regioselectivity (**2/2′**) is controlled not only by the ratio of $k/k′$ but also by the population of the productive conformers, $[K/(K + 1)]/[K′/(K′ + 1)]$, according to the Curtin–Hammett principle (blue lines in Figures 6 and 7). The switching of the mechanisms that determine the regioselectivity is responsible for the nonlinear Eyring

plots (red lines in Figures 6 and 7). In the reaction of 2-methylfuran, the higher substituted oxetane **2a′** is expected to form more than anticipated from the initial double-bond selection ($k/k′$) under the conditions of mechanism II, since the equilibrium constant $K′$ in **DR′** is *larger* than the equilibrium constant K in **DR** ($K′ > K > 1$, Scheme 9). Thus, the experimentally obtained Eyring plot (red line, Figure 6b) deviates from the green line (mechanism I, Figure 6a) at around −55 °C and approaches to the blue line with increasing the yield of the *higher* substituted oxetane **2a′** (mechanism II, Figure 6c). In the reaction of 3-methylfuran, the less-substituted oxetane **2b** is expected to form more than anticipated from the initial double-bond selection, since the population of the productive conformer **T−C1b′** in **DRb′** is *smaller* than that of the productive conformer **T−C1b** in **DRb**. Thus, the experimentally obtained Eyring plot (red line, Figure 7b) departs from the green line (mechanism I, Figure 7a) at around −50 °C and approaches to the blue line with increasing the yield of *lower* substituted oxetane **2b** (mechanism II, Figure 7c). The dramatic decrease of the quantum yield observed in the Paternò–Büchi reaction of 3-methylfuran (Figure 5) suggests the preferable formation of the inside-gauche conformer in the initial stage of the photochemical reaction.

Temperature Effects on Singlet and Triplet Photocycloadditions

The Eyring plots become even more complex than already described for pure triplet reactions when the carbonyl components can act as triplet as well as singlet excited substrates: in Figure 8, the temperature dependence of the product *diastereoselectivities* is given for three aliphatic aldehydes in the reaction with 2,3-dihydrofuran at 1.0 M initial concentrations. Additionally, the effect of concentration increase is shown for the propionaldehyde case (blue curves in Figure 8). In all cases, nonlinear plots with inversion regions were obtained.
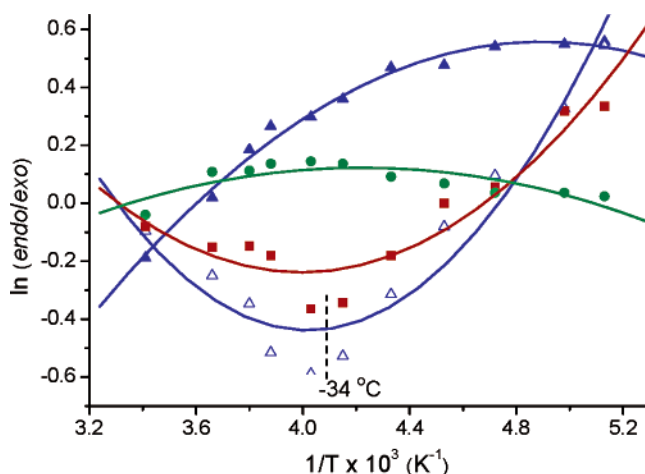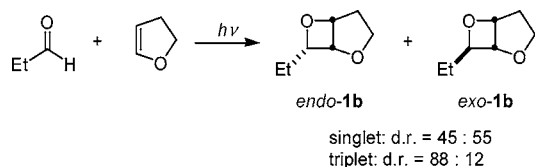

FIGURE 8. Eyring plots for photocycloaddition to 2,3-dihydrofuran at different substrate concentrations: (a) propionaldehyde, (▲) 1.0 M, (△) 5.0 M; (b) acetaldehyde, (■) 1.0 M; (c) isobutyraldehyde, (●) 1.0 M.

Scheme 10. Diastereoselectivity as an Indicator for Triplet versus Singlet Process

endo-**1b**   exo-**1b**

singlet: d.r. = 45 : 55
triplet: d.r. = 88 : 12

Scheme 11. Magnetic Isotope Effect (MIE) on a Triplet Photocycloaddition

endo-**1a**   exo-**1a**

for H: d.r. = 82 : 18
for D: d.r. = 90 : 10

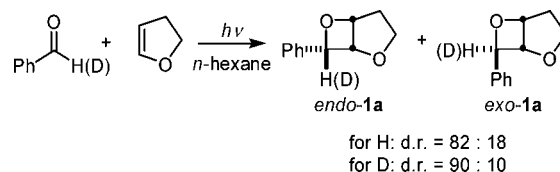**Scheme 12. Conformational Memory of Triplet Biradicals**

Modification of substrate concentrations can shift these regions, for example, where a normal behavior is observed for the propionaldehyde reaction at low concentrations (full triangles), an inversion effect for the *endo*-**1b**/*exo*-**1b** ratio appears at −34 °C when the initial concentration is increased (open triangles). The qualitative interpretation of these selectivity inversions is as follows: From the singlet channel, the activation barrier for the formation of the exo product is much smaller than that for the endo product (Scheme 10). However, the preexponential factor for the endo product is larger than that for the exo product. With decreasing temperature, the exponential part dominates and more exo product is formed than the endo product. The situation is completely different for triplet channel, namely, the formation of both the endo and exo products has almost no barrier (vide supra for the **2**/**2′** system), whereas the preexponential factors favor the formation of the endo product.

Both singlet and triplet channels compete with each other at 1.0 M concentration. With decreasing temperature, the triplet contribution increases. Due to larger endo/exo selectivity from the triplet channel (dr = 5.6) with decreasing temperature, the total endo/exo ratio increases steadily. Similar effects have been reported with *cis*- and *trans*-cyclooctene as substrates and aromatic (pure triplet systems),[31] as well as aliphatic, aldehydes.[32]

Isotope Effects on Singlet and Triplet Photocycloadditions

Studies of isotope effects are exceedingly important for our understanding of reaction mechanisms. With respect to photochemical processes, isotope effects have less often been applied,[33] partly due to the larger difficulties in determining reaction rate constants. Furthermore, the appearance of different spin states, which only slowly interconvert, presents an additional degree of complexity. As already stated by Turro and Kraeutler in a seminal review in 1980, tiny differences in the nuclear-spin hyperfine coupling constants (HFC) might lead to substantial differences in process where spin states are interchanging,[34] creating the concept of *spin chemistry* as defined and described in several reviews by Buchachenko.[35] In addition to the effects originating by the spin−orbit coupling induced ISC, additional effects arising from HFC differences might also contribute and manifest themselves in substantial *magnetic isotope effects* (MIE).[36] For ^{1}H/^{2}H pairs, significant MIE are expected since the HFC constants for ^{2}H are smaller by a factor of 6.5 for than those for protons.[37]

To evaluate isotope effects on the diastereoselectivity of "pure" triplet photocycloadditions, benzaldehyde and
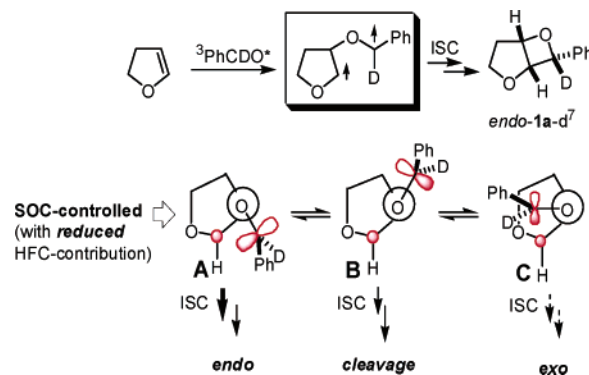
1-[2]H-benzaldehyde were used as carbonyl substrates.[38] With 2,3-dihydrofuran, the sensitive probe for spin selectivity, solvent properties, and reaction temperature, the reaction with PhCHO results in a endo/exo mixture of oxetanes **3** with the endo-diastereoisomer preferred.

From several runs, an average isotope selectivity effect of 2.8 for the [2]H-benzaldehyde/dihydrofuran reaction was determined (Scheme 11), defined as (*endo*-**1a**-*d*[7])(*exo*-**1a**)/(*exo*-**1a**-*d*[7])(*endo*-**1a**).[39] This effect on k_H/k_D might also be due to reduced triplet benzaldehyde lifetime (and consequently a higher singlet contribution). For aliphatic aldehydes, however, α-deuteration has been reported to result in an increase in triplet lifetime.[40] An alternative explanation is an amplification of the cleavage channel from the intermediate 1,4-triplet biradical. We have determined the quantum yield for the photocycloaddition of benzaldehyde to 2,3-dihydrofuran as 0.45.[39] Thus, the cleavage channel can compete with product formation with similar probability in the nondeuterated case. On the other hand, the lifetime of triplet 1,*n*-biradicals has been reported to slightly increase upon perdeuteration.[41]

In Scheme 12, gauche and anti conformers for the intermediate 1,4-biradical from dihydrofuran and a triplet benzaldehyde are shown. We originally postulated a strong preference for the **A** conformer as the decisive species for endo product formation due to a combination of strong SOC and minimization of group repulsion.[19]

One can safely assume that H/D exchange does not influence the energies of the ISC-reactive conformers **A**−**C** or the SOC constants. In the case of deuterated substrates, however, due to the lower HFC contribution,[37] the SOC-induced stereoselectivity is expected to become strengthened. Because SOC is already the dominating mechanism, these magnetic isotope effects are only moderate but clearly detectable.

Conclusion

We have made significant progress in elucidating the relationship between regio- and diastereoselectivity and the spin inversion process in triplet 2-oxatetramethylene biradicals through a combination of experimental and theoretical studies. Significant and sometimes surprising temperature, solvent, isotope, and substituent effects were observed. Most surprising from the viewpoint of a classical understanding of organic reaction mechanisms involving single-state reactivity is that very weak intramolecular interactions such as spin−orbit coupling (SOC, some calories per mole)−in systems carrying no heavy atoms− or hyperfine coupling (HFC, some millicalories per mole)− in the absence of strong external magnetic fields−can strongly participate in influencing the reaction diastereoselectivity. In the corresponding *singlet* reactions, the diastereoselection process is born out of the enthalpy differences between the two terminal C−C bond forming trajectories (if at all a two-step process is involved). Starting with the fully equilibrated *triplet* biradicals, the formation of closed-shell products, however, requires spin inversion and with that, the selectivity of the product formation becomes spin-related. The $\Delta\Delta G^{\ddagger}$ for the formation of diastereoisomers in the Paternò−Büchi reaction involves several kilocalories per mole due to steric and stereoelectronic interactions in the specific conformers that are prone to undergo intersystem crossing. Thus, *very weak interactions* connected with spin inversion processes can lead to *substantial control* of regio- and diastereoselectivity.

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