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Substantial ^{2}H-Magnetic Isotope Effects on the Diastereoselectivity of Triplet Photocycloaddition Reactions

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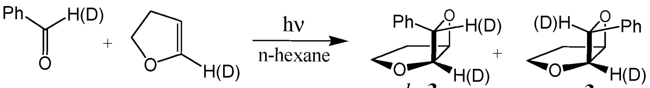
Studies of isotope effects are exceedingly important for our understanding of reaction mechanisms.[1] Primary and secondary kinetic isotope effects (KIE) as well as equilibrium isotope effects (EIE) are frequently analyzed as valuable tools. In recent years, spectacular reinvestigations of numerous basic organic reactions have been performed by Singleton and co-workers using natural abundance isotope distribution demonstrating the significance of these effects.[2] Less often have isotope effects been used in photochemical reactions,[3] partly due to the larger difficulties in determining reaction rate constants. Furthermore, photochemical reactions present an additional degree of complexity: the appearance of different spin states which only slowly interconvert. As was already stated by Turro and Kräutler in a seminal review in 1980, differences in the nuclear-spin hyperfine coupling constants (HFC) might lead to substantial differences in a process where spin states are interchanging.[4] This speculation has created a new concept, spin chemistry, as is defined and described in several reviews by Buchachenko.[5] In recent publications,[6] we have described spin chemistry effects in photocycloaddition reactions which were generated by spin−orbit coupling (SOC) phenomena determining the geometries of triplet biradical intermediates when crossing into the singlet potential hypersurface.[7] Spin−orbit coupling is thought to be the dominant factor for triplet biradicals connected by short hydrocarbon chains as in tetramethylenes or in 2-oxatetramethylenes, and geometrical factors strongly influence SOC.[8] This concept has recently been supported by theoretical calculations of the conformational dependence of SOC in triplet 2-oxatetramethylenes.[9] We now demonstrate that additional effects arising from HFC differences might also contribute and manifest themselves in substantial magnetic isotope effects (MIE).[10] For ^{1}H/^{2}H pairs, significant MIEs are expected because the HFC constants for ^{2}H are smaller by a factor of 6.5 than those for protons.[11]

Scheme 1. Paternò−Büchi Reactions of **1**, **1**-*d*, **2**, **2**-*d*



1 **2** *endo*-**3** *exo*-**3**

H/H	82 : 18
D/H	93: 7
H/D	89 : 11
D/D	90 : 10

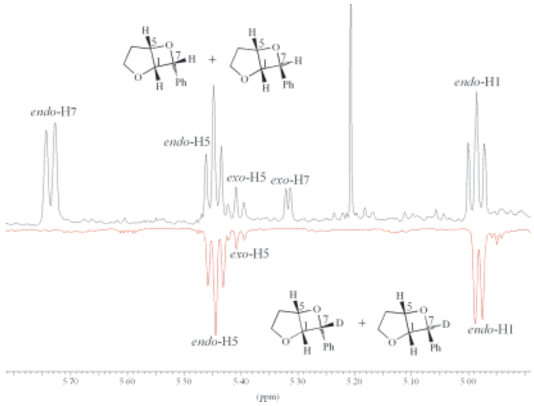


Figure 1. ^{1}H NMR spectra of **3** and **3**-*d*:[7] top trace, region for H-1, H-5, and H-7 for **3**; bottom trace, **3**-*d*.[7]

To evaluate isotope effects on the diastereoselectivity of "pure" triplet photocycloadditions, benzaldehyde (**1**) and 1-^{2}H-benzaldehyde (**1**-*d*)[12] were used as carbonyl substrates. As olefinic reaction partners, we applied 2,3-dihydrofuran (**2**) and 5-^{2}H-dihydrofuran (**2**-*d*).[13] As further olefinic substrates, we used several substituted cycloalkenes. Dihydrofuran shows high endo-selectivity in triplet Paternò−Büchi reactions;[14] the latter substrates gave significantly lower diastereoselectivity. The photochemical reactions were performed under conditions identical to those of **1** and **1**-*d*, and the endo/exo-ratios were determined by ^{1}H NMR and GC/GC-MS analyses; for reactions with **1**-*d*, the reactions were determined additionally by ^{2}H NMR analysis. For 2,3-dihydrofuran (**2**), a sensitive probe for spin selectivity,[14] solvent properties,[15] and reaction temperature,[16] the reaction with **1** results in an endo/exo mixture of oxetanes **3** with the endo-diastereoisomer preferred. From the GC/MS-analyses of the crude reaction mixtures of the three possible substrate combinations, a significant isotope effect on the noninduced diastereoselectivity, that is, the endo/exo-ratio, was determined (Scheme 1). For all combinations between deuterated and nondeuterated substrates, an increase in stereoselectivity was observed. The combination of **1**-*d* and **2**-*d* did, however, not result in an additional effect. From several runs, we determined an average isotope selectivity effect of 2.8 for the ^{2}H-benzaldehyde/dihydrofuran reaction (**1**-*d*/**2**), defined as (endo **3**-d_7) × (exo **3**)/(exo **3**-d_7) × (endo **3**). In Figure 1, the proton trace of one deuterium-containing oxetane mixture is shown together with the nonlabeled products **3**. To obtain further information on kinetic isotope effects, we determined the reactivity differences between **1** and **1**-*d* competing for the alkene **2**. The k_H/k_D values from ^{1}H NMR analyses for competition reactions with initial concentrations of 1:1:1 and 2:2:1 for **1**:**1**-*d*:**2** were 1.05 and 1.1, respectively. Thus, deuterated benzaldehyde **1**-*d* is only slightly less reactive with **2** than **1**, but gives significantly higher diastereomeric ratios. The effect on k_H/k_D might also be due to reduced triplet benzaldehyde lifetime. For aliphatic aldehydes, however, α-deuteration has been reported to result in an increase in triplet lifetime.[17] An alternative explanation is an amplification of the cleavage channel from the intermediate 1,4-triplet biradical. We have recently estimated the quantum yield for the photocycloaddition of benzaldehyde (**1**) to 2,3-dihydrofuran (**2**) as 0.45.[16] 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.[18] Assuming that the isotope effect on the stereoselectivity is

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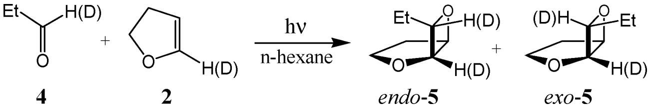
connected with triplet biradical behavior only, a spin-correlation effect was expected on the endo/exo-ratio of Paternò−Büchi photocycloadditions of aliphatic aldehydes capable of reacting from both their singlet and their triplet excited states. Indeed, propionaldehyde (**4**) as the carbonyl component shows a pronounced spin-correlation effect.[14] We have now additionally investigated the concentration dependence of the noninduced diastereoselectivity for the deuterated aldehyde **4**-*d*[19] and the combination of **4** with **2**-*d* (Scheme 2).

Scheme 2. Paternò−Büchi Reactions of **2**, **2**-*d*, **4**, **4**-*d*



In the triplet region (low substrate concentration), a similar isotope effect on the endo/exo-ratio was determined for the **2**-*d*/**4** and the **2**/**4**-*d* combinations (Figure 2). An average isotope selectivity effect (as defined above) of 1.2 resulted for both reactions at 0.01 M. These results originate from several factors, all in connection with intersystem crossing processes: ISC rates are reduced, and thus singlet as well as triplet lifetimes are increased. This effect seems to be balanced out for the **2**/**4** reaction: the inversion regions are nearly identical for all combinations.

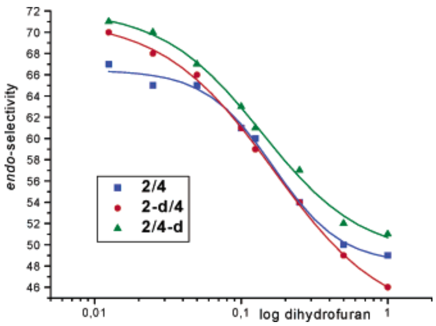
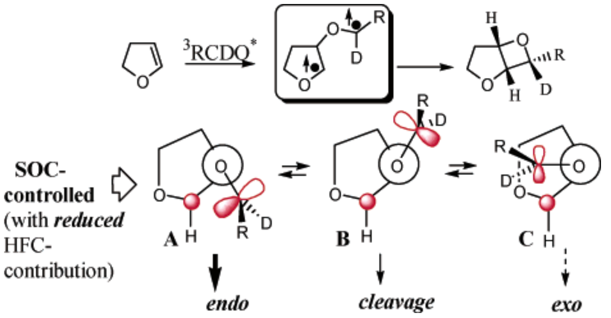


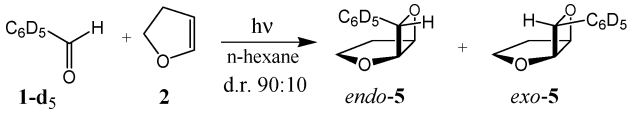
Figure 2. Concentration/selectivity profiles for the photocycloaddition of EtCHO with **2** (blue) and deuterated substrate combinations.

Scheme 3. Conformers of 1,4-Biradical Intermediates



In Scheme 3, gauche and anti conformers for the intermediate 1,4-biradical from dihydrofuran and a triplet carbonyl are shown. We originally postulated[7] a strong preference for the **A** conformer as the decisive species for endo-product formation due to a combination of strong SOC[9] and minimization of group repulsion. Additional sterically encumbering groups at C-5 reduced the diastereoselectivity due to the contribution by conformer **C**.[20] From photocycloadditions of substituted cycloalkenes with **1**-*d*, low isotope selectivity effects of 1.1−1.2 were determined, whereas unsubstituted cycloalkenes (as **2**) gave higher effects of 1.9−3.0. Cyclohexene, for example, gave a selectivity increase upon change to deuterated benzaldehyde **1**-*d* from 74:26 to 85:15. We assume that H/D exchange does not influence the energies of the ISC-reactive conformers **A**−**C** nor the SOC constants. In the case of deuterated substrates, however, due to the lower HFC contribution,[11] 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. Furthermore, the fact that similar MIEs were detected for the combinations **1**/**2**-*d* and **1**-*d*/**2** strongly argues for the intermediacy of 2-oxatetramethylenes (OTM) as triplet biradicals and against a 1-OTM structure which was discussed as an alternative in recent theoretical publications.[21] A significantly weaker MIE is expected from the **1**-*d*/**2** reaction via a 1-OTM biradical. That a MIE is operative became also clear from the result of the photocycloaddition of the pentadeuterated aldehyde **1**-d_5 [22] with **2** (Scheme 4).

Scheme 4. Paternò−Büchi Reaction of d_5-Benzaldehyde with **2**



As compared to **1**-*d*, a slightly weaker but still significant isotope selectivity effect of 1.9 was determined for this system.

Acknowledgment. This study was initiated by a comment from Peter R. Ogilby (University of Århus). He called our attention to the pronounced difference in ^{1}H and ^{2}H nuclear-spin electron-spin coupling and the potential consequences.

Supporting Information Available: Substrate preparation, NMR data, and NMR traces of the photocycloaddition reactions (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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