Diastereomeric Discrimination in the Lifetimes of Norrish Type II Triplet 1,4-Biradicals and Stereocontrolled Partitioning of Their Reactivity (Yang Cyclization versus Type II Fragmentation)


Abstract: The stereochemistry at C2 and C3 carbons controls the partitioning of triplet 1,4-biradicals of ketones among various pathways. Differences in the major reaction pathways, for example, cyclization (syn) and fragmentation (anti), adopted by the diastereomeric 1,4-radicals of ketones have permitted unprecedented diastereomeric discrimination in their lifetimes to be observed by nanosecond laser flash photolysis. From quantum yield measurements and transient lifetime data, the absolute rate constants for cyclization and fragmentation of a pair of diastereomeric triplet 1,4-biradicals have been determined for the first time.

Keywords: diastereoselectivity · ketones · photolysis · radicals

Introduction

Conformational control of reactivity of intermediates can be achieved, in principle, by restricting their mobility. This has been achieved environmentally (for example, intermolecularly) in several ways. An extreme is reaction within the neat crystalline state in which lattice forces can control the fates of intermediates generated both thermally and photochemically.[1] Usually, less specific environmental control is exerted when reactions are conducted in “container” systems, such as cyclodextrins,[2] calixarenes,[3] cucurbiturils,[4] etc.[5] in zeolites[6] with well-defined cavities, or in liquid crystals[7] and in polymer films[8] with less well-defined and more dynamic cavities.[9] An entirely different approach, involving intramolecularly designed control, which has been adopted by us[9] entails the imposition of steric interactions about contiguous chiral centers, such that the resulting diastereomers exhibit distinct conformational preferences; reactions in which the diastereomers exhibit differing reactivities are termed “diastereomer-differentiating”.[10] This strategy has been exploited to demonstrate a remarkable diastereomeric discrimination in triplet lifetimes of a diketone.[11]

Scheme 1 is a paradigm for Norrish–Yang Type II reactions.[12] Initial γ-hydrogen abstraction from the triplet states of aromatic ketones (R1 = phenyl) leads to a cisoid conformation for the 1,4-biradicals. A subsequent twisting motion about the C1–C2 bond is necessary to attain another cisoid conformation (shown in Scheme 1), a requisite for cyclization, in which the two singly-occupied orbitals are directed toward each other. Although the fragmentation products may derive from both cisoid and transoid conformations, the fragmentation is generally ascribed to transoid conformations.[12,13] While the geometries of triplet 1,4-biradicals (1BR) appear to control the product profiles, there is no clear understanding until now of how they partition themselves among the various pathways shown in Scheme 1.[14] In view of this, understanding of the factors that influence the lifetimes of triplet 1,4-biradicals (1BR), which are also intermediates in reactions, such as Paterno–Büchi and ene-olefin photocycloadditions,[15] and their behavior[16] continues to be of significant contemporary interest.[17] Insofar as
the Norrish Type II reaction is concerned, its potential as applied to photorelease processes, asymmetric synthesis, etc. has begun to unfold only recently.

We have recently shown that different triplet lifetimes, caused by conformational preferences intrinsic to the diastereomers of \( a,\beta \)-disubstituted ketones, such as 1, can lead to reactivity differences. In this instance, rapid Yang cyclization and Norrish Type II fragmentation, accentuated by the formation of thermodynamically stable styrene/stilbene products (\( R = \text{Me/Ph} \)), precluded direct observation of the intermediary triplet 1,4-biradicals by nanosecond transient absorption spectroscopy and, hence, incontrovertible evidence for the hypothesized link between diastereomeric discrimination and biradical lifetimes. In pursuit of the latter, we designed ketones 2 based on the following rationale: 1) the 3\( \beta \)-BR of 2 are bisbenzylic and hence should be relatively longer lived than those of 1 and 2) they should be less prone to fragment, further increasing the 3\( \beta \)-BR of 2 with respect to those of 1 with \( R = \text{Ph} \) (in which fragmentation leads to a thermodynamically more stable alkene).

Here, we report the results of our investigation involving the unprecedented diastereomeric discrimination in 3\( \beta \)-BR generated by irradiation of the diastereomeric \( \alpha,\beta \)-dimethyl-\( \gamma \)-phenyl-butyrophenones 2 and stereoccontrolled partitioning of their reactivity between Yang cyclization and Norrish Type II fragmentation. Furthermore, and perhaps of even greater mechanistic importance, the absolute rate constants for the cyclization and fragmentation pathways of the diastereomeric 3\( \beta \)-BR have been calculated from lifetime and quantum yield measurements. The subtle differences among the rates provide unprecedented insights into the relationships among the competing processes.

**Results and Discussion**

The diastereomers of ketone 2 were synthesized by 1,4-addition of MeMgI to PhCOC-(CH\(_3\))=CHCH\(_2\)Ph. Because the separation of the two diastereomers could not be achieved by silica-gel chromatography using a variety of solvent systems, an indirect route was followed. The diastereomeric mixture was first reduced with NaBH\(_4\) to afford a mixture of four diastereomeric alcohols, which could be separated fractionally by TLC using diethyl ether/petroleum ether 25:75 as eluent. Gravity column chromatography of the mixture afforded three alcohols (one as a mixture), which upon oxidation yielded pure syn and anti isomers of ketone 2. Configurational assignment of the diastereomers was based on comparisons of \( ^1H \) NMR spectroscopic chemical shifts of the 3\( \beta \)-methyl carbon atoms of the analogous ketones reported in the literature. Furthermore, the \( \alpha \)-methyl carbon atoms of the syn and anti diastereomers of analogous ketones have been noted in the literature to exhibit distinct \( ^13C \) NMR spectroscopic chemical shifts: the signal from the \( \alpha \)-methyl carbon of the analogous syn diastereomer appears approximately 2–5 ppm further upfield than that of the anti. Thus, the \( ^13C \) NMR signal from the \( \alpha \)-methyl carbon of the diastereomer of 2 assigned as syn based upon the \( ^1H \) NMR spectroscopic chemical shifts appears at 15.1 ppm, while that of the anti diastereomer resonates at 17.8 ppm. Cyclization and fragmentation photoproducts accounted for >90% of consumed ketone when the diastereomers of 2 were irradiated (\( \lambda_{\text{irrad}} \approx 350 \) nm) at approximately 25°C in solvents, such as chloroform, cyclohexane, etc. Whereas irradiation of the syn diastereomer led mostly to cyclization products (approximately 66% relative yield) with >90% diastereoselectivity as indicated by \( ^1H \) NMR spectroscopy, the anti diastereomer afforded predominantly fragmentation products (>85% relative yield, Scheme 2). The cyclobutanol (CB) from the syn diastereomer was isolated from a preparative-scale irradiation, characterized by
IR and \(^1\)H and \(^{13}\)C NMR spectroscopies, and its stereochemistry was deduced from NOESY experiments (see Supporting Information).

Irradiations of both diastereomers in cyclohexane were examined in detail in view of their very different \(\rho_{BR}\) in this solvent (vide infra). Thus, photoproduct distributions from approximately 0.03 \(\text{m}\) cyclohexane solutions of each diastereomer in NMR tubes under nitrogen atmospheres were determined directly by \(^1\)H NMR spectroscopy using the homonuclear gated decoupling (hmg) technique. The cyclization/fragmentation product ratio was approximately 2:1 from the \(\text{syn}\) diastereomer and 15:85 from the \(\text{anti}\) (Scheme 2). The cyclobutanol shown in Scheme 2 from the \(\text{anti}\) isomer was detected in very low yield (approximately 6–7\%), and its isolation from a preparative photolysis of approximately 1 \text{mmol} of the ketone was complicated by formation of a nearly equal amount of an inseparable second cyclobutanol derived by means of hydrogen abstraction from the \(\beta\)-methyl group. The major fragmentation pathway for the \(\text{anti}\) does not involve the “minor” \(^3\)BR resulting from the abstraction of hydrogen from the \(\beta\)-methyl group, because \(\beta\)-methylstyrene (along with propiophenone) is the almost exclusively detected fragmentation alke (Scheme 2); very little (if any) 3-phenylpropene, the olefin expected from fragmentation of the “minor” 1,4-biradical, was detectable by \(^1\)H NMR spectroscopic analyses. Thus, with a maximum limit of 7\% relative yield for the cyclobutanol from the “major” 1,4-biradical and 85–87\% yield for fragmentation, the cyclization/fragmentation ratio is estimated to be 1:10. Furthermore, the disappearance quantum yields (\(\Phi\)) for the \(\text{syn}\) and \(\text{anti}\) diastereomers upon irradiation at 313 nm in cyclohexane \(^{25}\) were determined to be 0.52 ± 0.02 and 0.31 ± 0.02, respectively.

Laser flash photolyses (XeCl excimer laser, 308 nm and 10 ns pulses of 80 mJ energy) of solutions of the diastereomers of \(\text{2}\) in a number of solvents led to transient absorption spectra, such as those in Figure 1. The transient spectra are virtually identical in position and shape, as expected. Each has the attributes of a benzylic/ketyl radical \(^{26}\) a strong absorption (OD ca. 0.05–0.10) at 310–320 nm and a weak, broad absorption with a shoulder in the region around 400–470 nm. Also, the absorption was efficiently quenched by oxygen, and the decay times of the transients are similar to those reported for a 1,4-biradical from \(\gamma\)-phenylbutyrophefone in MeOH (146 \pm 19 ns) and in a low polarity solvent, such as heptane (55 \pm 8 ns) \(^{27}\). Based upon these observations, the transient absorptions in Figure 1 are attributed to \(^3\)BR from the diastereomers of \(\text{2}\) \(^{28}\).

The decays monitored at 320 and 420–440 nm were clearly monoexponential and had the same decay constants. The lifetimes thus determined for the diastereomeric \(^3\)BR of \(\text{2}\) in a variety of solvents are collected in Table 1. Small differences in the lifetimes for the diastereomeric biradicals were observed in a number of polar and low-polarity protic and aprotic solvents. However, an unprecedented discrimination in the \(\tau_{BR}\) was found in cyclohexane, a relatively viscous and low-polarity solvent \(^{29}\). In at least six independent determinations, the \(\tau_{BR}\) from the two diastereomers reproducibly ex-

Scheme 2. Mechanistic rationalization of distinct photochemical fates observed for \(\text{syn}\) and \(\text{anti}\) diastereomers of ketone \(\text{2}\).
transoid 2006 specifically, the denounced, was observed in two mixed solvent systems, mately 30% of the average. A similar trend, albeit less pro-

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<th>syn-2 (ns)</th>
<th>anti-2 (ns)</th>
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<tr>
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<td>134</td>
<td>142</td>
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<tr>
<td>2</td>
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<td>n-hexane</td>
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<td>8</td>
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[a] Monitoring wavelength = 320 nm. [b] Error = ± 5%.

hibited a lifetime difference of 15 ns, representing approximately 30% of the average. A similar trend, albeit less pronounced, was observed in two mixed solvent systems, βBuOH/ethylene glycol 3:2 and benzene/water 95:5. More specifically, the tBR from the syn diastereomer (which decays to cyclobutanol as the major product) were consistently shorter than those from the anti (which fragments principally).

The 3BR may decay by three possible unimolecular pathways, denoted by kE, kF, and kC in Scheme 1, which involve intersystem crossing.[12,15] As mentioned earlier, there is still no clear understanding of how biradical structure affects its partitioning among the three pathways,[14] although certain structural features of biradical reactivity are established.[12,13] We have recently shown that the diastereomer-differentiating photochemical reactions of 1 can be rationalized based on 1) stereoregulated stabilization of the geometry (cisoid/transoid) of the 3BR and 2) the premise that cyclization will be observed only if a 3BR assumes a cisoid geometry while fragmentation occurs predominantly from the transoid geometry.[19]

We apply similar considerations to 2 as well (Scheme 2, double arrows signal steric congestion). The steric interac-

tions between the α,β-dimethyl substituents should cause conformational preferences of the ketones such that their respective 3BR, generated subsequent to photolysis, are also similarly influenced. Furthermore, steric repulsions between the C2 and C3 methyl substituents must disfavor the attainment of a cisoid conformation of the anti 3BR; the confor-
mational preference and the source of most reactivity should be from the transoid conformation. The opposite conformational preference (and source of reaction) is predicted by the same steric arguments for the syn 3BR; the cisoid conformation must be favored energetically. Thus, the observed predominant fragmentation from the anti diastereomer and high cyclization yields from the syn diastereoisomer are in accord with expectations based on simple arguments for stereochemical preferences of the diastereomers of 2 and their 1,4-biradicals. Although the cisoid conformer may, in principle, lead to fragmentation, it is less likely because of the stringent stereoelectronic require-

ments,[13] involving the overlap of the singly-occupied orbitals at C1 and C4 with the C2–C3 sigma orbitals and the steric crowding that this geometry entails.

Inherent to the stereoregulated partitioning of the dia-
estereomeric biradical reactivity discussed above is the possi-

bility to observe differential rates for their decay. The two tBR, especially in cyclohexane, demonstrate that their very different chemical fates (for example, predominantly frag-

mentation or cyclization) occur at distinctly different rates; although the observed differences in the tBR are small such a discrimination has not been heretofore scrutinized. By using a simplified form of the mechanism in Schemes 1 and 2, in which kE refers to fragmentation from both the transoid and cisoid 3BR precursors, the experimentally-deter-

dined 3BR decay rate constants and absolute rate con-

stants for each of the reactive pathways followed by the dia-
estereomeric triplet 1,4-biradicals can be calculated from dis-

appearance quantum yields and the relative cyclization and fragmentation photoproduct yields.

As the triplet states of phenyl alkyl ketones and the triplet 1,4-biradicals are formed with unit efficiency,[12,13] the quantum yields for fragmentation (ΦF) and cyclization (ΦC) are given by: ΦF = kF/C0 and ΦC = kC/C0, in which kE, kC, and kF are the rate constants for fragmentation, cyclization, and reversion of the 3BR to 2, respectively. Accordingly, kE = kF and kC = kF.

Based on the relative product ratios for the two diastereoisomers, the total quantum yield for ketone disappearance (ΦF + ΦC), the decay constants in cyclohexane (1/tBR), and the absolute rate constants for cyclization and fragmentation of the diastereomeric 3BR are calculated to be: kE = 0.46×10^s s−1, kF = 4.6×10^s s−1, and kC = 7.5×10^s s−1, kE = 3.8×10^s s−1. As 1/tBR = (kF + kE), the values are calculated to be 11.5×10^s s−1 (anti) and 11.3×10^s s−1 (syn). Clearly, the difference in the overall quantum yields for consumption of the two diastereoisomers of 2 is governed by their rates of cycli-

zation; the values of kE and kF are nearly the same for the two diastereoisomers! These data demonstrate the importance of diastereocoroll over the conformations of the 1,4-biradicals.

Figure 1. Transient absorption spectra attributed to 3BR derived from syn-2 (●) and anti-2 (●) in cyclohexane after a pulse delay time of 35 and 65 ns, respectively. Inset shows the decay profiles monitored at 320 nm (slow for anti and fast for syn) of the diastereomeric 3BR; the relatively higher OD after the decay of the biradical in the case of the anti diastereomer is unquestionably due to stronger absorbance of the derived frag-

Table 1. Lifetimes of 3BR (ns) derived from the diastereomers of 2[a,b]

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[a] Monitoring wavelength = 320 nm. [b] Error = ± 5%.
Conclusion

We have shown that the partitioning of the 1BR between cyclization (cisoid) and fragmentation (transoid) pathways can be controlled by means of steric interactions built around substituents at C2 and C3 of ketone 2. The two diastereomeric 1BR derived from irradiation of 2 collapse by distinct pathways—cyclization, fragmentation and return to 2—that can be discriminated kinetically to correlate structure and reactivity with unprecedented detail. To the best of our knowledge, these are the first absolute rate constant determinations for cyclization and fragmentation of a pair of diastereomeric triplet 1,4-biradicals. These results offer extremely detailed insights into the motions that triplet 1,4-biradicals must undergo to decay to singlet ground-state products. Clearly, other substitution patterns will expand our knowledge of the motions of 1,4-biradicals.

Experimental Section

Preparation of α,β-dimethyl-γ-phenylbutyrophenones 2: The required precursor α,β-unsaturated ketone, namely 1,4-diphenyl-2-methyl-2-butenone, was prepared according to the procedure already reported by us.[9]

Methyl iodide (10.09 g, 71.16 mmol) was added to the Mg turnings (1.7 g, 71.16 mmol) suspended in dry ether (50 mL) followed by a catalytic amount of iodine. The reaction mixture was warmed up and stirred overnight at room temperature. The reaction was quenched with saturated NH4Cl and extracted with EtOAc. The organic layer was washed with brine solution, dried over anhydrous Na2SO4, and the solvent removed in vacuo. The crude diastereomeric mixture (syn and anti) in approximately 32% yield.

NaBH4 reduction of the mixture of diastereomers of 2 and reoxidation of separated alcohols

To the mixture of diastereomers (0.930 g, 3.69 mmol) in EtOH (40 mL) was added NaBH4 (0.084 g, 2.21 mmol). After refluxing for 2 h, the reaction mixture was quenched with 10% aqueous HCl (10 mL) and the volume was reduced to approximately 20 mL. The resulting mixture was extracted with EtOAc and the organic layer was washed with brine solution, dried over anhydrous Na2SO4, and concentrated in vacuo. The crude diastereomeric mixture of the alcohols, isolated in near quantitative yields (>96%) was purified by silica gel column chromatography (diethyl ether/petroleum ether 2:1) and identified as a mixture of diastereomers (syn and anti) in approximately 32% yield. The required product was purified by column chromatography on silica gel (EtOAc/hexane 20:80). The crude product was recrystallized by using valerophenone as an actinometer (Φmax = 0.33 for the formation of acetophenone).[25] For quantum yield measurements, a solution of a diastereomer of ketone 2 in cyclohexane (approximately 0.04 M) was irradiated by using high-pressure Hg lamp (Applied Photophysics) equipped with a monochromator. Conversion of the ketones was limited to 15–16% and analyses were performed by gas chromatography.

LASER FLASHPHOTOLYSIS: Experiments were carried out with an LKS60S nanosecond laser flash photolysis spectrometer (Applied Photophysics) with a GSI Lumonics PulseMaster PM-846 excimer laser running on XeCl for excitation (308 nm, approximately 80 mJ pulse energy, 10 ns pulse width). The transient data were recorded with a 54830B 600 MHz Infinium oscilloscope (Agilent Technologies) and processed with the instrument-supplied software. Transient spectra were recorded in a step-scan mode in 10 nm intervals. Transient decay traces were recorded near the transient absorption maxima at approximately 320 and 450 nm. Samples (approximately 3 mL) were prepared in fused long-neck quartz cuvettes to allow bubbling with dry nitrogen gas for 15 min to remove oxygen. The optical densities of all samples were adjusted to 0.4 ± 0.1 at 308 nm by using a Cary50 UV spectrophotometer (Varian).

Acknowledgements

J.N.M. is grateful to Department of Science and Technology (DST, India) and the Alexander von Humboldt (AvH) Foundation (Germany) for supporting a collaborative effort at the International University Bremen, Bremen. The US National Science Foundation is thanked for its support, allowing R.G.W. to participate in this project.


[30] No correction for the small component of the anti diastereomer involving abstraction of a methyl hydrogen has been included in the calculations.

Received: June 22, 2006
Published online: August 25, 2006