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1,5-Biradicals and Five-Membered Rings Generated by δ-Hydrogen Abstraction in Photoexcited Ketones

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Introduction

The past decade has witnessed a remarkable upsurge of interest among synthetic organic chemists in the preparation of five-membered rings by "non-ionic" processes, in particular, photocycloadditions[1] and radical cyclizations.[2] One such method that has not yet been widely scrutinized involves the coupling of 1,5-biradicals.

Biradicals have been the subject of increasing interest over the past 20 years, particularly with regard to the factors that determine the lifetimes of triplet biradicals.[3] Most studies related to this point have involved one of three photochemical methods for generating biradicals: sensitized decomposition of cyclic azo compounds;[4] α-cleavage of cyclic ketones;[5] and intramolecular hydrogen abstraction by ketones.[6-8] In fact there have been two Accounts devoted to 1,4-biradicals formed by γ-hydrogen abstraction: an early description of the evidence for the intermediacy of biradicals[9] and a more recent study of biradical lifetimes.[6]

This Account describes the 1,5-biradicals resulting from intramolecular hydrogen abstraction by triplet ketones. The goals of this work were twofold: (1) to determine the potential utility of photoinduced intramolecular hydrogen transfer for the synthesis of five-membered rings and (2) to learn more about triplet biradicals, specifically by comparing the behavior of 1,5-biradicals to that of the 1,4-biradicals already studied. Both goals require an understanding of the factors that control the efficiency of biradical cyclization; the first also requires learning the factors that affect triplet state δ-hydrogen atom abstraction. We have found that irradiation of appropriate ketones often leads to five-membered rings but that the intermediate 1,5-biradicals undergo a greater variety of competitive reactions and show rather different lifetime variations than do the "smaller" 1,4-biradicals.

Background Studies

It has been known for 20 years that the facile photoelimination reaction[10] of ketones with γ-C–H bonds involves 1,4-biradicals generated by excited state γ-hydrogen abstraction.[8,11] Cyclization of these 1,4-biradicals to cyclobutanols usually is only a minor process[12,13] but can become dominant when the competing

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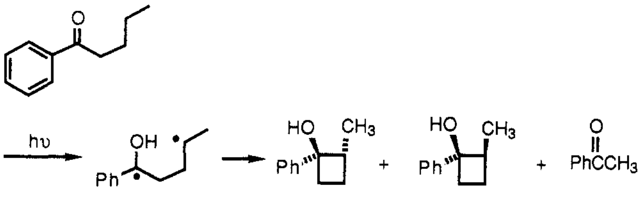
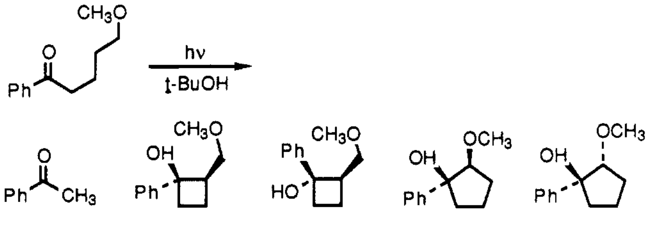
cleavage reaction is slowed by conformational, stereoelectronic factors.[14]



benzene	3.5%	14.5%	82%
alcohol	4%	8%	88%

Before 1972 there were only a few scattered reports of photoinduced cyclopentanol formation involving primarily ketones that have no γ-hydrogens and very reactive δ-C–H bonds.[15-19] Despite these reports, it was widely believed that straight-chain alkanones undergo photoinduced internal hydrogen abstraction only at the γ-carbon. This presumed regiospecificity was explained in terms of the well-known preference for 1,5-hydrogen transfers in radical chemistry.[20] We then showed that cyclopentanol formation does compete evenly with type II reactions in δ-alkoxy[21] ketones; the results indicated a 20:1 γ:δ preference for hydrogen abstraction from unactivated methylenes,[22] much the same rate constant ratio found for intramolecular hydrogen atom abstraction in alkoxy radicals.[23] We also showed that the efficiency of cyclization of the 1,5-biradicals formed by δ-hydrogen atom abstraction is often very low. Therefore the overall quantum efficiency of cyclopentanol formation from straight-chain ketones is low even when δ-hydrogen abstraction is a competitive excited-state reaction. For example, the quantum efficiency of cyclopentanol formation from δ-methoxyvalerophenone is only 10% even though over 50% of the triplets form a 1,5-biradical.[21] It thus became important to determine which reactions of 1,5-biradicals compete so well with cyclization.



Φ = .37 .06 .03 .015 .085

Conformational Effects on Excited-State Reactivity

Intramolecular photoreactions can occur from rotationally equilibrated conformations or only from ground-state conformations, depending on how decay rates and rotational rates compete.[24-26] We have established in a series of studies that intramolecular reactivity in acyclic triplet ketones is governed by normal conformational factors,[25] in this case the entropy and enthalpy of forming transition states of different ring size. This topic has been addressed most recently by Dorigo and Houk,[27] whose calculations accurately reproduce the experimental preference for 1,5- vis 1,6-hydrogen atom transfers and emphasize the lower entropy for formation of the smaller cyclic transition state.

Scheme I

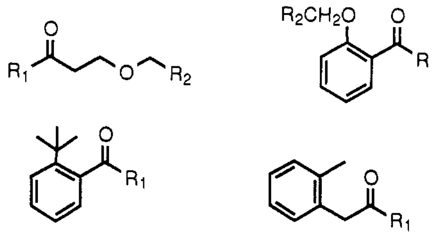
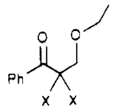
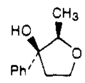
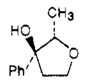


Table I
Quantum Yields for Product Formation from 1

	hν	 +	
X = H	benzene	0.40	0.09
	t-BuOH	0.13	0.16
X = D	benzene	0.52	0.12
	t-BuOH	0.23	0.31

Whatever exact balance between entropy and enthalpy[22] determines the γ/δ preference in acyclic triplet ketones, it is obvious that cyclopentanol formation cannot be efficient when the ketone has reactive γ-C–H bonds. Therefore the only ketones that might undergo efficient photocyclization to five-membered rings are those with either unreactive or nonexistent γ-C–H bonds. There are very few examples of the former. The inductive effects of substituents can alter δ/γ reactivity only so much, to 2:1 in γ-benzoylbutyraldehyde[28] and 1:1 in δ-methoxyvalerophenone.[21] In cyclic systems, however, conformational effects produce huge variations in hydrogen abstraction rate constants.[25,29] Thus cyclodecanone undergoes only ϵ-hydrogen abstraction.[30] Paquette's synthesis of dodecahedrane relied on several δ-hydrogen abstractions by cyclopentanone units.[31] The rigid geometry of the polycyclic precursors forces a δ-hydrogen close to the carbonyl and holds the γ-hydrogens far away.

This Account will concentrate on ketones with no γ-hydrogens. The structural types studied are portrayed in Scheme I. It turns out that several of these systems have provided new examples of significant conformational effects on both triplet and biradical reactivity.

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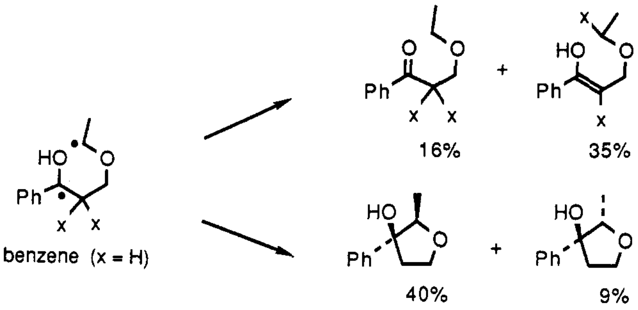
Acyclic β-Alkoxy Ketones

We thoroughly investigated the photochemistry of β-ethoxypropiophenone (1) in order to characterize the formation and behavior of 1,5-biradicals in acyclic systems.[32] Its only photoproducts are the two diastereomeric oxacyclopentanols.

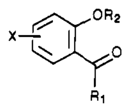
Biradical Behavior. The key features of the photochemistry of 1 are the solvent and isotope effects listed in Table I. The *Z*:*E* product ratio depends strongly on solvent polarity, showing little selectivity in Lewis base solvents but strongly favoring the isomer with the methyl trans to the phenyl in benzene. However, alcohol solvents do not raise the cyclization quantum efficiency substantially. Hydrogen bonding of the OH in 1-hydroxy 1,4-biradicals to solvent molecules that are Lewis bases *always* suppresses disproportionation back to ground-state ketone, thus maximizing product quantum yields, and also increases the effective bulk of the OH group, thus lowering the diastereoselectivity in cyclization.[13,33] The 1-hydroxy 1,5-biradicals apparently also hydrogen bond to basic solvents and thus lose selectivity in cyclization. The isotope effects on quantum yields and the H–D exchange between the α- and δ-carbons in unreacted 1 indicate that the lower-than-100% product quantum yields reflect competing disproportionation at the α-CH to form the enol of starting ketone. Interestingly, this mode of biradical disproportionation, with $k_H/k_D = 3$, accounts for 70% of the total reversion in undeuterated 1.



There are no examples of 1,4-biradicals disproportionating to the enol of starting ketone. Of course, such disproportionation would involve a 1,3-hydrogen transfer that would not be expected to compete with the observed 1,5-transfer. In a 1,5-biradical, 1,4-transfer at CH obviously would be subject to less strain than a 1,3-transfer in the shorter biradical. What is surprising is that it is faster than a 1,6-transfer at OH, which is almost the reverse of the process that formed the biradical! It is known that 2-hydroxy-2-propyl radicals disproportionate with preferential formation of acetone enol rather than acetone itself.[34] The similar CH vs OH selectivity in 1,5-biradicals indicates that the impediment to monoradical 1,4-hydrogen atom transfers is less important in biradical disproportionations. Apparently C–H–C linearity is not as important in the highly exothermic biradical reaction as it is in the only slightly exothermic simple H atom transfers.

We presume that the low quantum yields of cyclopentanol formation observed for other cases of δ-hydrogen abstraction in phenyl alkyl ketones[22] also are caused by substantial 1,5-biradical disproportionation to enol of starting ketone. Fortunately this competing enolization lowers only the quantum yield, not the chemical yield; the enols reketonize rapidly. In fact this photoenolization may provide another way to generate enols for kinetic study.[35]

Table II
Photoreactivity of *o*-Alkoxyphenyl Ketones in Benzene



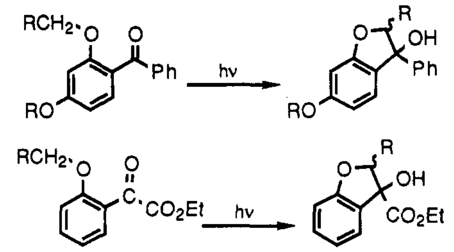
ketone	R_1	R_2	X	$k_{\delta\text{-H}}$, s^{-1}	Φ_{cyc} (*Z*:*E*)
2	Ph	CH_3	H	5×10^5	0.30
3	Ph	CH_3	6-OCH_3	2×10^5	–
4	Ph	CH_3	3-PhCO	1×10^7	0.77
5	Ph	CH_2Ph	H	2×10^7	0.95 (7.5) 0.5 (1.1)[a]
6	CH_3	CH_3	H	$<10^5$	<0.01
7	CH_3	CH_2Ph	H	2×10^6	0.023 (10) 0.20 (1)[a]
8	CH_3	CH_2Ph	3-CH_3CO	2.5×10^7	0.17
9	*n*-Bu	CH_2Ph	H	(2×10^6)	0

[a] With added pyridine.

Triplet Reactivity. The reciprocal triplet lifetime of 1, presumably the rate constant for δ-hydrogen abstraction by its n,π* lowest triplet, is 2×10^7 s^{-1}. This value is large enough that no physical decay processes compete. However, the addition of electron-donating[36,37] or π-conjugated electron-withdrawing[38] substituents to the benzene ring would produce π,π* lowest triplets and consequently would lower the observed rate constant sufficiently that quenching by impurities or solvent would become competitive. Good chemical yields would still be possible provided that a chemically unreactive solvent such as acetonitrile were used.

o-Alkoxyphenyl Ketones

Several *o*-alkoxybenzophenones[17] and (*o*-alkoxyphenyl)glyoxalate esters[16] have been reported to undergo photocyclization to benzodihydrofuranols.



No kinetics had been measured for the former compounds, which often give unusual byproducts; so we undertook a systematic investigation.[39] Table II contains some representative data. The most important general findings are that acetophenones are much less reactive than benzophenones and give more byproducts; even the benzophenone triplets have small rate constants for δ-hydrogen abstraction. Thus *o*-methoxy-

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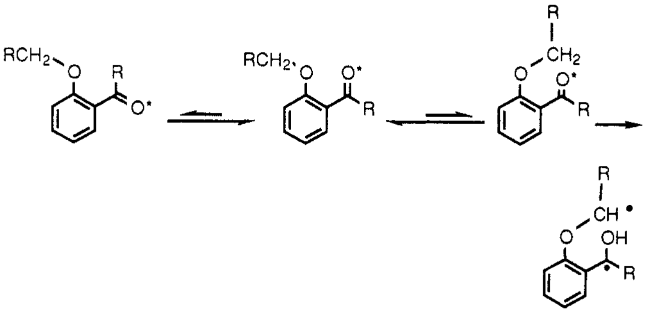
acetophenone (**6**) does not photocyclize; *o*-(benzyloxy)valerophenone (**9**) undergoes only Norrish type II photoelimination; and *o*-methoxybenzophenone (**2**) undergoes photoreduction as well as photocyclization in hexane and methanol.

Triplet Reactivity. The low rate constants for δ-hydrogen abstraction in these ketones clearly are due to conformational factors, in particular a low equilibrium population of the rotamer in which the alkyl group of the *o*-alkoxy is syn to the carbonyl. The fact that *o*-benzyloxy ketones are much more reactive than *o*-methoxy ketones, as expected by their relative C–H bond strengths, indicates that reactions are not limited by bond rotation rates but rather involve rotational equilibrium prior to rate-determining hydrogen abstraction.[25,26] 2,6-Diacyl methoxy and benzyloxy compounds such as **4** and **8** all display triplet reaction rates at least 10 times greater than those for the monoketones. This fact substantiates the unfavorable rotational equilibrium about the benzene–oxygen bond mentioned above. The comparable reactivities of 2-alkoxy and 2,6-dialkoxy ketones (e.g., **2** and **3**) indicate that the triplets achieve rotational equilibrium about the benzene–carbonyl bond before reaction, as expected[40] for such unreactive triplets, and that this equilibrium favors the reactive rotamer.

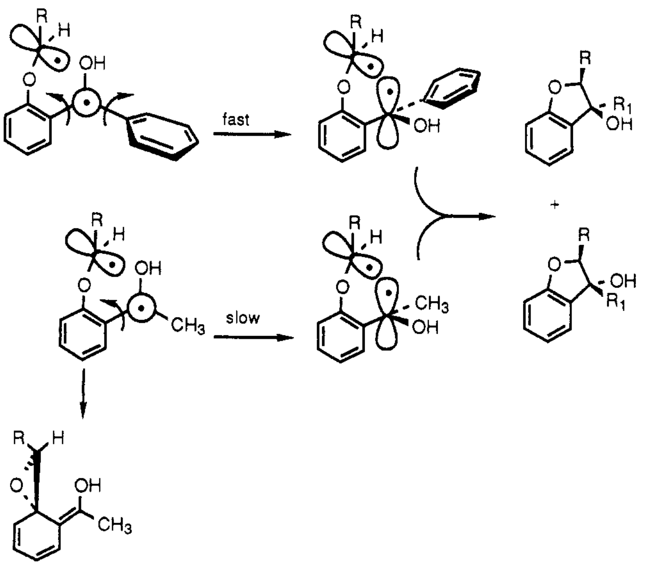


The incorporation of a ring between the carbonyl and the hydrogen being attacked often enhances abstraction rate constants by an order of magnitude because of the decreased loss of rotational entropy in the transition state.[29] An example involving γ-hydrogen abstraction is *o*-methylacetophenone (3×10^9 s^{-1})[40] vs γ-phenylbutyrophenone (4×10^8 s^{-1}).[42] The analogous comparison for δ-hydrogen abstraction is **2** ($<10^6$ s^{-1}) vs **1** (2×10^7 s^{-1}).[32] The ring in these *o*-alkoxy ketones *decreases* reactivity by an order of magnitude relative to the acyclic case! This factor of 100 difference from expectations is another indication of the unfavorable rotational equilibrium mentioned above.

All of the benzophenones studied have n,π^* lowest triplets. The significantly lower $k_{\delta\text{-H}}$ values observed for the *o*-alkoxyacetophenones reflect their π,π^* lowest triplet configurations.[37a] Any further $^3\pi,\pi^*$-stabilizing substitution would lower rate constants so much that hydrogen abstraction would occur only in very low quantum efficiency.

Biradical Behavior. Product yields and distributions depend strongly on solvent and differ dramatically for acetophenones and benzophenones. *o*-(Benzyloxy)benzophenone (**5**) cyclizes with almost 100% efficiency in benzene, less in the presence of Lewis bases such as pyridine.[43] Such behavior is just the opposite of what has been recorded for all other 1,4- and 1,5-hydroxy biradicals. Here the *unsolvated* biradical undergoes almost no reverse hydrogen transfer. The solvated biradical (so established by the large drop in *Z*:*E* cyclization ratio) apparently undergoes some other reaction competitive with cyclization to an oxaindanol. The original study of this reaction noted the same phenomenon in the production of phenols as byproducts in alcohol solvents;[17] (*o*-alkoxyphenyl)glyoxalate esters also suffer polar solvent induced diminution of cyclization quantum yields.[16]

In the presence of added pyridine, *o*-(benzyloxy)acetophenone cyclizes with a 10-fold-higher efficiency than in pure benzene, but at the expense of stereoselectivity. Such behavior is what is normally expected for hydroxy biradicals.[13] Most of the quantum inefficiency is due to the low rate constant for δ-hydrogen abstraction, on top of which only 10% of the unsolvated 1,5-biradicals cyclize. The large difference in this regard between the benzophenone and the acetophenone has no parallel in other hydrogen abstraction reactions and has been ascribed to a competing spirocyclization. The competition between oxaindanol formation and spirocyclization is determined by the ease of rotation about the benzene–benzyl radical bond in the biradical, which is fast in the benzophenone-derived biradical but slow in the acetophenone biradical.[43] This competition represents another unique example of conformational restrictions on a reactive intermediate. The phenols and diketones formed as byproducts probably result from air oxidation of the presumed spiroenol intermediate.[43]



o-*tert*-Butylphenyl Ketones

Triplet Reactivity. The slowness of triplet ketone δ-hydrogen abstraction from *o*-alkoxy groups was hinted at by an early report that 2-*tert*-butyl-4,6-dialkoxybenzophenones abstract hyrogen only from the *tert*-butyl group.[18] That such hydrogen abstraction may be very rapid was suggested by the refusal of *o*-*tert*-butylvalerophenone to undergo the type II reaction.[44]

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[40] Wagner, P. J.; Chen, C.-P. *J. Am. Chem. Soc.* **1976**, *98*, 239.

[41] This footnote was deleted on revision.

[42] Wagner, P. J.; Kemppainen, A. E. *J. Am. Chem. Soc.* **1972**, *94*, 7495.

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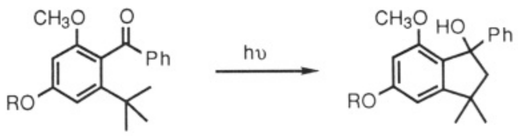
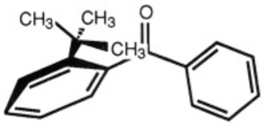


A careful study of *o-tert*-butylbenzophenone itself (**10**) confirmed that δ-hydrogen abstraction by the triplet is remarkably fast, with $k^{25°} \approx 10^9$ s^{-1} in methanol and greater in hydrocarbon solvents.[45] Arrhenius parameters for triplet decay in methanol are $E_a = 2.4$ kcal/mol and log $A = 10.6$. Extrapolation to 77 K predicts a rate constant of 10^4 s^{-1}; indeed, indanol is formed even at this low temperature.

The acyclic analogue γ,γ-dimethylvalerophenone (**11**) undergoes triplet-state δ-hydrogen abstraction with a rate constant of only 3×10^5 s^{-1}.[22] The 4 order of magnitude enhancement that results from freezing out a single bond rotation in **10** is remarkable. This large rate constant for attack on an intrinsically unreactive primary C–H bond presumably results from the molecule being in a perfect geometry for reaction when excited. The crystal structure of **10** reveals that the *tert*-butyl group is indeed perfectly aligned for reaction, with the *tert*-butylbenzene ring twisted 70° out of coplanarity with the carbonyl and the molecule itself having only a limited number of conformations. In fact, crystalline **10** undergoes photocyclization quite efficiently, indicating that the 1,5-biradical either is formed properly aligned for cyclization or can easily rotate.



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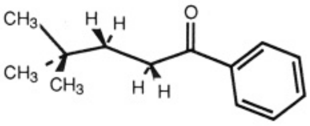

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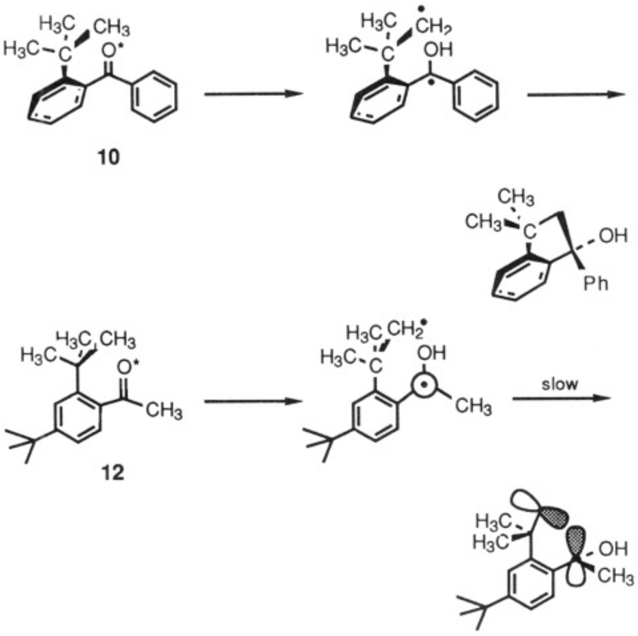
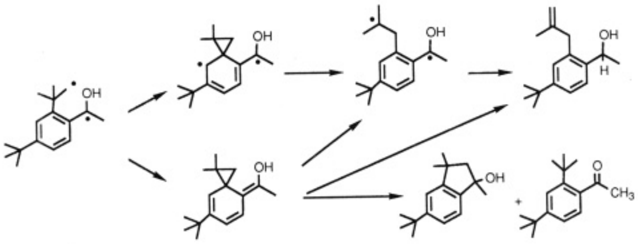
Biradical Behavior. Triplet *o-tert*-butylbenzophenones all react so rapidly that the intermediate 1,5-biradicals are easily detectable by flash spectroscopy. The lifetime of the biradical from **10** is very solvent dependent, increasing with solvent polarity from a value of <4 ns in hydrocarbons to 43 ns (invariant from −100 to 25 °C) in methanol. Paramagnetic quenchers such as oxygen and nitroxides shorten its lifetime, as is commonly observed for triplet biradicals.[46] Decay of the biradical produces a yellow byproduct in <1% yield, for which a spiroenol structure has been suggested. Product quantum yields also show a large solvent effect, increasing from only 0.05 in hydrocarbon to 1.0 in methanol. The solvated biradical cyclizes very efficiently.

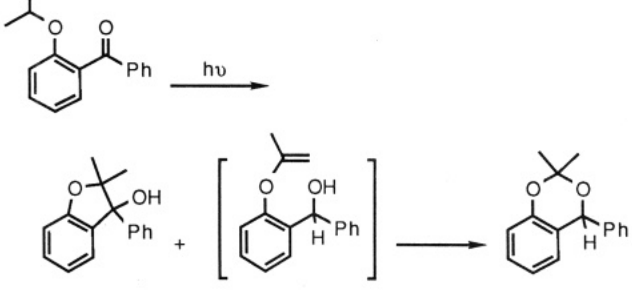
2,4,6-Tri-*tert*-butylacetophenone also undergoes photocyclization to an indanol, albeit in quite low quantum efficiency.[47] To our surprise, 2,4-di-*tert*-butylacetophenone (**12**) gives only a 10% yield of indanol, the major product being a 1-(*o*-isobutenylphenyl)ethanol.[48] Compound **12** has a π,π^* lowest triplet and shows a much longer triplet lifetime (26 ns in toluene) than does **10**. Nonetheless, it is still too reactive for the low quantum yield of product formation to be attributed to competing triplet decay.



The *tert*-butylbenzoyl group of *triplet* **12** is more nearly coplanar than it is in **10**.[48] Therefore the initially formed 1,5-biradical must undergo a large rotation around the bond connecting the benzyl radical center to the benzene ring in order to form an indanol. As noted above, such a rotation is relatively slow. Therefore we have suggested that the main reaction of the biradical is cyclization of the δ-radical site onto the ortho position to generate a spiroenol. This could be an adiabatic reaction, with the triplet trienol opening to the more stable, isomeric biradical, which can disproportionate to the major product. Alternatively, the spirotrienol may undergo competing sigmatropic hydrogen shifts to give product or ground-state reactant.



o-Isopropoxybenzophenone has been reported to undergo a similar internal redox photorearrangement.[17] Bis tertiary 1,5-biradicals appear to resemble radical pairs in that disproportionation competes well with cyclization.



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(45) Wagner, P. J.; Giri, B. P.; Scaiano, J. C.; Ward, D. L.; Gabe, E.; Lee, F. L. *J. Am. Chem. Soc.* **1985**, *107*, 5483.

(46) (a) Encinas, M. V.; Scaiano, J. C. *J. Photochem.* **1979**, *11*, 241. (b) Small, R. D.; Scaiano, J. C. *J. Am. Chem. Soc.* **1978**, *100*, 4512. (c) Small, R. D., Jr.; Scaiano, J. C. *J. Phys. Chem.* **1977**, *81*, 828.

(47) Ditto, S. R.; Card, S. J.; Davis, P. D.; Neckers, D. C. *J. Org. Chem.* **1979**, *44*, 894.

(48) Wagner, P. J.; Giri, B. P.; Pabon, R.; Singh, S. B. *J. Am. Chem. Soc.* **1987**, *109*, 8104.

Table III
Photokinetics of ArCH(R)COZ in Benzene

ketone	Ar	R	Z	$1/\tau$, 10^8 s^{-1}	Φ_α[a]	Φ_{II}[b]	Φ_δ[c]	Φ_{EE}[d]
13	o-tolyl	H	Ph	1.6	0	-	1.0	-
14	o-tolyl	CH_3	Ph	0.5	0.28	-	0.05	-
15	o-tolyl	n-Pr	Ph	1.8	0.03	0.12	0.015	-
16	mesityl	H	Ph	11.0	0	-	0.55	-
17	mesityl	CH_3	Ph	2.9	0.02	-	0.24	0.01
18	mesityl	n-Pr	Ph	10.0	0.02	0	0.12	0.005
19	mesityl	H	mesityl	7.3	0.35	-	-	-
20	mesityl	$(CH_3)_2$	Ph	7.0	0.31	-	-	-

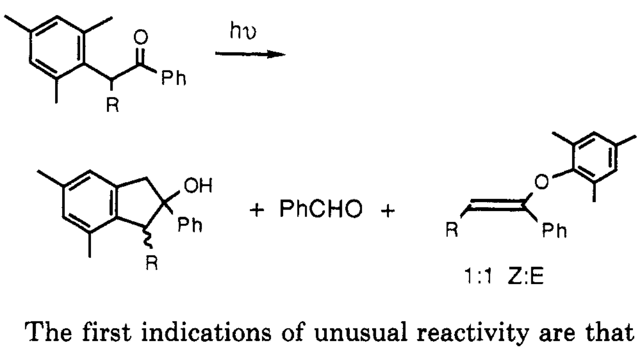
[a] Yield of benzaldehyde trapped by 0.01 M $C_{12}H_{25}SH$. [b] Yield of α-substituted acetophenone. [c] Yieldof indanol. [d] Yield of enol ether.

In the case of tri-*tert*-butylacetophenone, the ground state is twisted almost 90°[49] and hydrogen abstraction generates a biradical in a proper geometry for indanol formation, as is the case for **10**. Products are determined by differences in ground-state geometry only when excited states or biradicals formed from them are subject to restricted rotational freedom.

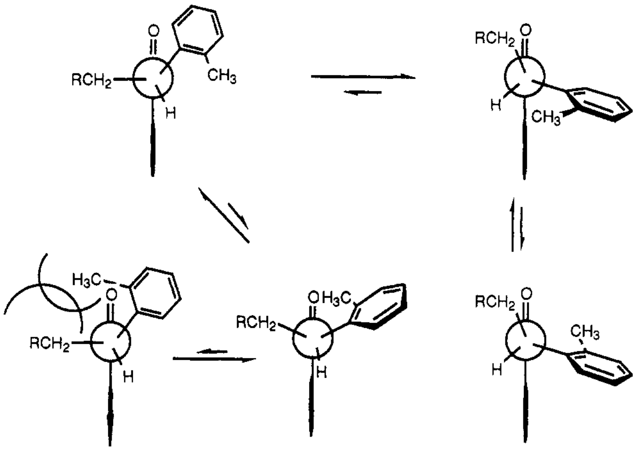
α-*o*-Tolyl Ketones

Such compounds had not been studied until we found that several simple α-*o*-tolyl- and α-mesitylacetophenones photocyclize very efficiently to 2-indanols.[50] Their triplets react very rapidly ($k > 10^8$ s^{-1}) such that the 1,5-biradical intermediates are readily detectable by flash spectroscopy.[51] However, not all such ketones form indanols efficiently. The *o*-alkyl groups produce steric congestion around the carbonyl, such that further substitution produces dramatic changes in product composition and excited-state kinetics. In fact, the behavior of these compounds provides a unique example of how rotational restrictions can limit photoreactivity.

Triplet Reactivity. These ketones undergo three competing triplet reactions: δ-hydrogen abstraction leading to indanol and/or enol; α-cleavage leading to radicals; and 1,3-aryl migration leading to enol ether.[52] Table III lists triplet lifetimes and quantum yields for various ketones. The rate constant for each reaction can be estimated by multiplying the triplet lifetime by the maximized quantum yield for each process.[53]



The first indications of unusual reactivity are that α-*o*-tolylvalerophenone (**15**) undergoes primarily the Norrish type II reaction and no cyclization to an indanol, while α-*o*-tolylpropiophenone (**14**) undergoes primarily α-cleavage and only 4% cyclization. The effective rate constant for δ-hydrogen abstraction in these two ketones is only 1/60 what it is in **13**. This rate reduction is not an inductive effect, since α-phenylvalerophenone undergoes triplet γ-hydrogen abstraction 70% as fast as does valerophenone itself.[54] Both X-ray studies and MM2 calculations indicate that the most stable conformations for all of these α-aryl-α-alkylacetophenones have the alkyl group, rather than the aryl, nearly eclipsing the carbonyl. In contrast, the favored ground-state conformation of α-mesitylacetophenone (**16**) has a benzylic C–H bond almost perfectly aligned for abstraction by the excited carbonyl. Thus α-substitution reduces the likelihood that an ortho-benzylic H atom is within abstracting distance[55] of the carbonyl. The low rate constants for δ-hydrogen abstraction reflect the nonbonded interactions that increase the energies of the reactive ground-state conformations.



α-Mesitylvalerophenone (**18**) does not undergo type II reaction; like α-mesitylpropiophenone **17**, it abstracts δ-hydrogens with lowered rate constants in competition with both α-cleavage and rearrangement to an enol ether. Now an added complication arises: NMR studies show that rotation of the mesityl group around the bond connecting it to the α-carbon is very slow (10^4 s^{-1}) on the excited-state time scale.[54] Nonbonded interactions between an *o*-methyl and an α-alkyl cause the mesityl to twist, such that even when the mesityl is nearly eclipsing the carbonyl, the benzylic C–H bonds are not at the best angle with respect to the carbonyl n-orbital. However, both MM2 calculations and X-ray structure determination indicate that this geometry is disfavored with respect to the one with the α-alkyl group nearly eclipsing the carbonyl, in contrast to the nearly ideal geometry of **16**. Therefore the relatively high efficiency of δ-hydrogen abstraction in **17** and **18** requires explanation.

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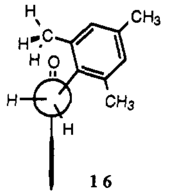
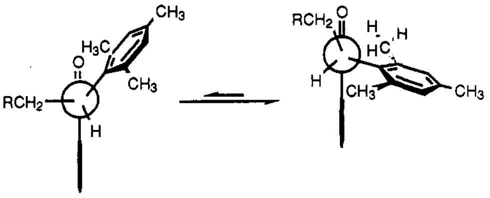
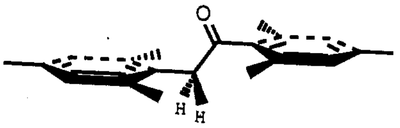
(49) Leibfritz, D. *Chem. Ber.* **1975**, *108*, 3014.
(50) Meador, M. A.; Wagner, P. J. *J. Am. Chem. Soc.* **1983**, *105*, 4484.
(51) Scaiano, J. C.; Wagner, P. J. *J. Am. Chem. Soc.* **1984**, *106*, 4626.
(52) Wagner, P. J.; Zhou, B. *J. Am. Chem. Soc.* **1988**, *110*, 661.
(53) Wagner, P. J.; McGrath, J. M. *J. Am. Chem. Soc.* **1972**, *94*, 3849.
(54) Hasegawa, T.; Wagner, P. J., unpublished work.
(55) Scheffer, J. R.; Czakpasu, A. A. *J. Am. Chem. Soc.* **1978**, *100*, 2163.



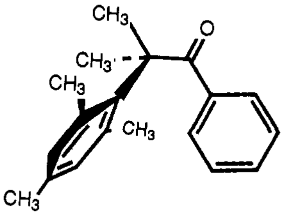
16



Two types of ketones undergo only α-cleavage; 1,2-dimesitylethanone (**19**) and α,α-dimethyl ketones such as **20**. The X-ray crystal structure and MM2 calculations both indicate that the two mesityl groups of **19** lie parallel to each other but perpendicular to the carbonyl, perfectly aligned for radical cleavage but with all C–H bonds too far from the carbonyl oxygen for hydrogen transfer to take place. NMR line broadening studies on **20** indicate that rotation around the α-carbon–carbon bond is slow ($<10^5$ s^{-1}) on the excited-state time scale and that the two α-methyls are not equivalent in the most stable conformation. α-Cleavage to a tertiary benzylic radical is now so fast that the excited molecules do not have time to rotate into a conformation suitable for δ-hydrogen abstraction.



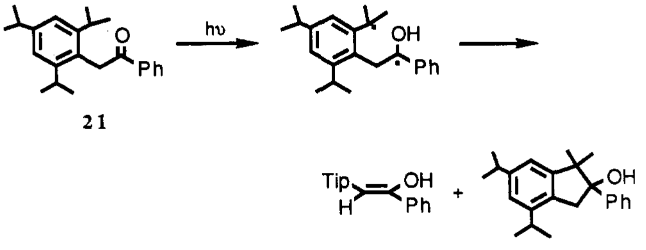
19



20

Biradical Behavior. The 1,5-biradicals formed from several of these ketones have been characterized by flash spectroscopy.[51] They all have lifetimes in the 15–40-ns range that vary only slightly with solvent polarity. They undergo little reversion to ground-state ketone, since quantum yields are high and do not depend much on solvent, equalling unity in the case of α-tolylacetophenone.

Several ketones were tested for photoenolization. Irradiation of α-mesitylacetophenone-α-d_2 produces no H–D exchange between the α-carbon and the benzylic carbons. In contrast, the enol is the major product from α-(2,4,6-triisopropylphenyl)acetophenone (**21**),[56] with its yield depressed by α-deuteration. The biradical is formed just as fast as that from the mesityl ketone but apparently encounters too much steric hindrance in trying to cyclize. It is interesting that the indanol yield is much higher in benzene than in dioxane. The ether is known to solvate hydroxy biradicals and, in this case, has the usual effect of suppressing cyclization. This photoenolization may not be very general, since more congested ketones such as 1,2,2-trimesitylethanone, that are known to be less stable than their enol forms,[57] photorearrange to an enol ether rather than undergoing δ-hydrogen abstraction.[58]



4:1 Z:E

Solid-State Reactivity. Most of these ketones react in the solid state, generally forming even higher yields of indanol than in solution. Crystalline **17** and **18** give only indanol with no cleavage or enol ether. Irradiation of crystals of **14** gives a 67% yield of indanol compared to the mere 15% obtained in solution. Mattay has found that detergents similarly enhance indanol yield from several α-o-tolylalkanones, which normally undergo only α-cleavage.[59]

Much of the enhanced indanol yields must be due to immobilization and forced recombination of the radical pairs formed by α-cleavage. Nonetheless, indanol formation could not occur unless these ketones exist in geometries that allow formation via δ-hydrogen abstraction of biradicals in conformations that can then cyclize without too much molecular motion. This fact is most striking for **18**. Its crystal structure looks poor for δ-hydrogen abstraction, since the propyl group eclipses the carbonyl. One of the o-methyls lies in the shielding region of the benzoyl group with a hydrogen within 2.5 Å of the oxygen. However, H and O define a line almost perpendicular to the axis of the oxygen n-orbital. It is widely believed that n,π^* hydrogen abstraction is facile only when the hydrogen lies close to that axis ($\theta = 0$).[60] Scheffer has reported several crystalline reactions where the hydrogen lies 30–60° above the nodal plane of the carbonyl π-system.[28,55] I have even suggested that the rate constant should show a $\cos^2\theta$ dependence.[61] In **18**, θ is 70°, and reaction certainly occurs readily. Moreover, the biradical formed from this geometry is perfectly aligned to cyclize.

Given the great difficulty in making quantitative measurements on solids, the observation of efficient photocyclization merely indicates that hydrogen abstraction can occur at an unknown rate even when the hydrogen overlaps much better with the π-orbital than with the n-orbital. However, the fact that δ-hydrogen abstraction occurs in solution with a rate constant of 10^8 s^{-1}, one-fifth that for **16** in its ideal geometry, strongly suggests that hydrogen abstraction occurs primarily from the geometry with $\theta = 70°$ ($\cos^2\theta = 0.11$). Other examples of such "out-of-plane" hydrogen

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[56] Wagner, P. J.; Meador, M. A. *J. Am. Chem. Soc.* **1984**, *106*, 3684.

[57] Fuson, R. C.; Rowland, S. P. *J. Am. Chem. Soc.* **1943**, *65*, 992. (b) Biali, S. E.; Rappoport, Z. *J. Am. Chem. Soc.* **1985**, *107*, 1007.

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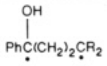
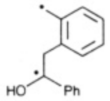
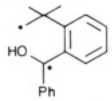
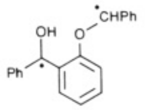
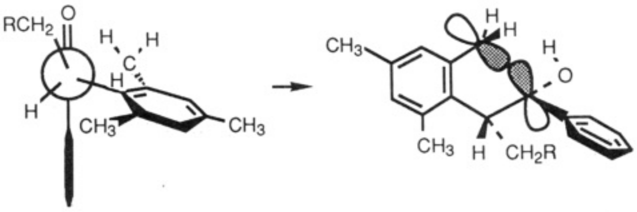
[61] Wagner, P. J. *Top. Curr. Chem.* **1976**, *66*, 1.

Table IV
Biradical Lifetimes[a] and Cyclization Efficiencies at 25 °C

biradical	τ, ns (Φ)		E_a, kcal	ref
	CH_3OH	alkane		
 $PhC(OH)^{\bullet}(CH_2)_2C^{\bullet}R_2$	100–300 (1)[b]	30–100 (0.3)[b]	~0	6, 7
	15 (1)	15 (1)	1	51[c]
	43 (1)	~4 (0.05)	0	45
	14 (0.5)	<4 (1)		43

[a] In nanoseconds. [b] Total type II products. [c] Wagner, P. J.; Johnston, L.; Scaiano, J. C., unpublished data.

abstraction by ketone triplets in the solid state also have appeared recently.[62]



Does Product Formation Affect Biradical Lifetimes?

Near-zero activation energies[45,46] provide strong evidence that triplet biradical decay involves triplet → singlet intersystem crossing (isc).[6] Recent interpretations of biradical lifetimes[4e,5–8,64] all focus on how isc rates may vary with structure or solvent. Conversely, most discussions of variations in the distribution of products formed from biradicals invoke classical structural and solvent effects on barriers to reactions.[65,66] Scaiano attempted to address this seeming inconsistency by suggesting that product ratios represent relative isc rates of different biradical conformers followed by reactions faster than bond rotations, with no contribution from barriers to product formation.[8] It is the latter assumption that 1,5-biradical behavior opens to serious question.

The 1,5-biradicals produced by δ-hydrogen abstraction greatly expand the number of structural types for which biradical lifetimes have been measured. Table IV compares solvent effects on these 1,5-biradicals to those already reported for typical Norrish type II biradicals. In all cases, Lewis base solvents increase biradical lifetimes only when solvation retards an otherwise dominant reaction such as disproportionation back to starting ketone or even cyclization. Scaiano has reported one experiment in which 1,4-biradical lifetimes and type II quantum yields do not increase in exact parallel as a function of added Lewis base, from which he concluded that the lifetime increase does not reflect slower chemical reaction but instead represents a polar solvent effect on isc.[67] However, Turro and Doubleday have shown that polar solvent effects on biradical lifetimes are restricted to hydroxy biradicals.[5a] We have now added two 1,5-biradicals that show large, parallel solvent effects on both lifetimes and quantum yields plus another biradical that shows no solvent effect on either, the quantum yield for cyclization being unity. *There certainly is no uniform "polar" solvent effect on isc.* The results require an enhanced explanation for variations in biradical lifetimes caused by structural as well as by solvent changes.

The concept of rate-determining isc for triplet biradical decay means either that subsequent product-forming reactions are faster than reverse isc or that product formation is concurrent with isc. The former possibility demands only that singlet biradicals react with activation parameters that would yield rate constants $>10^8\ s^{-1}$ (E_a = 2–3 kcal/mol; $A = 10^{10}$–$10^{11}\ s^{-1}$). Enol formation from **1** and **21** shows a primary isotope effect as large as observed in the disproportionation of 1-phenylethyl radicals.[68] This fact and the wide variations in product distributions for many different triplet-generated biradicals demand moderate barriers to product formation. In particular, all the hydroxy biradicals so far studied display strong diastereoselectivity when cyclizing in hydrocarbon solvents. Lewis base solvation reduces or eliminates this selectivity and fosters competitive disproportionation or spiroenolization, presumably because solvation increases the bulk of the OH group. Whatever process causes discrimination among possible product-forming modes responds to nonbonded interactions *in the developing products.* Therefore, if isc actually is involved in determining product distributions, isc must occur when the radical termini are within bonding distance. What Scaiano dubbed a "conformational memory" effect[8] in fact may be isc concurrent with product formation.

The latter situation almost certainly holds for the 1,5-biradicals formed from *o*-(benzyloxy)phenyl ketones. Like the 1,4-biradicals formed from α-alkoxy ketones,[5d,69] they have lifetimes too short to be measured by nanosecond flash kinetics. In these cases, biradical isc is so fast as to be competitive with bond rotations, and the biradicals respond to solvent effects in ways that correlate best with anticipated barriers to reaction.[70] If the 90° twist that brings the initially formed biradical into the correct geometry for cyclization also induces isc,[3] then cyclization could be almost concerted with rotation and the two rotations that produce diastereomeric biradicals may well proceed with different rates, given that the two stereocenters are being brought to within bonding distance of each other.

To what extent can this picture of concurrent isc and product formation hold for longer lived biradicals? The

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[62] (a) Chang, H. C.; Popovitz-Biro, R.; Lehav, M.; Leiserowitz, L. *J. Am. Chem. Soc.* **1987**, *109*, 3883. (b) Ito, Y.; Matsuura, T. *Tetrahedron Lett.* **1988**, *29*, 3087.

[63] This footnote was deleted on revision.

[64] (a) Zimmt, M. B.; Doubleday, C., Jr.; Gould, I. R.; Turro, N. J. *J. Am. Chem. Soc.* **1985**, *107*, 6724. (b) Zimmt, M. B.; Doubleday, C., Jr.; Turro, N. J. *J. Am. Chem. Soc.* **1985**, *107*, 6726. (c) Zimmt, M. B.; Doubleday, C., Jr.; Turro, N. J. *J. Am. Chem. Soc.* **1986**, *108*, 3618.

[65] Ariel, S.; Evans, S. V.; Garcia-Garibay, M.; Harkness, B. R.; Omkaram, N.; Scheffer, J. R.; Trotter, J. *J. Am. Chem. Soc.* **1988**, *110*, 5591.

[66] Zimmerman, R. G.; Liu, J. H.; Weiss, R. G. *J. Am. Chem. Soc.* **1986**, *108*, 5264.

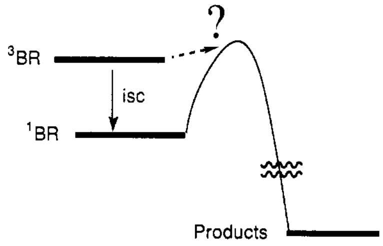
[67] Small, R. D., Jr.; Scaiano, J. C. *J. Phys. Chem.* **1977**, *81*, 2126.

[68] Gibian, M. J.; Corley, R. C. *Chem. Rev.* **1973**, *73*, 441.

[69] Freilich, S. C.; Peters, K. S. *J. Am. Chem. Soc.* **1981**, *103*, 6255.

[70] (a) Wagner, P. J.; Kemppainen, A. E. *J. Am. Chem. Soc.* **1968**, *90*, 5896. (b) Lewis, F. D.; Turro, N. J. *J. Am. Chem. Soc.* **1970**, *92*, 311. (c) Barton, D. H. R.; Charpiot, B.; Ingold, K. U.; Johnston, L. J.; Motherwell, W. B.; Scaiano, J. C.; Stanforth, S. *J. Am. Chem. Soc.* **1985**, *107*, 3607.

parallels in Table IV suggest such a possibility, and several CIDNP observations have been so interpreted.[71] Why would isc occur during rather than prior to product formation? If isc is not rapid unless the radical centers overlap, movement of the biradical termini along a reaction coordinate would induce isc and also enhance S–T splitting, such that the small activation energies for singlet biradical reaction are transformed into activation entropies for triplet biradical motion. Any additives that affect either isc or product formation then would affect both, as Scaiano has observed.[6] The question of the separation in time of isc and product formation certainly deserves more attention.



Summary

From a mechanistic standpoint, triplet ketone δ-hydrogen abstraction provides a variety of riches in terms of conformational effects on both triplets and 1,5-biradicals. Rate constants for triplet reaction vary over several orders of magnitude independent of intrinsic C–H reactivity. The probability of the biradicals cyclizing also varies tremendously, depending on environment as well as on any molecular restrictions to free rotation. From a synthetic standpoint, the reaction offers untapped potential but will have to be used with very careful planning because of the relatively large number of competitive reactions that 1,5-biradicals can undergo. Fortunately, irradiation in immobilizing media can minimize some competing triplet reactions.

I thank my various students, especially Michael Meador and Boli Zhou, whose Ph.D. theses describe all of our work on o-alkoxyphenyl and α-o-tolyl ketones, and Brij Giri, who performed the original work on o-tert-butyl ketones; Prof. Ken Houk for a preprint of his unpublished work and stimulating discussions; and Dr. Tito Scaiano at the National Research Council in Ottawa for his enthusiastic cooperation in the measurement of flash kinetics data.

Registry No. H, 1333-74-0.

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[71] (a) Doubleday, C. *Chem. Phys. Lett.* **1981,** *79,* 375. (b) Kaptein, R.; DeKanter, F. J. J.; Rist, G. H. *J. Chem. Soc., Chem. Commun.* **1981,** 499.

Comparative Reactivities of Hydrocarbon C–H Bonds with a Transition-Metal Complex

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Alkanes are among the most abundant and unreactive of all organic compounds. Industrial use of these resources often relies upon free-radical activation of carbon–hydrogen bonds, often at high temperatures, thereby limiting the selectivities that can be achieved in any functionalization reaction.[1] Consequently, the selective activation of C–H bonds by homogeneous transition-metal compounds has been a topic that has been of great interest to the organometallic community for many years.[2]

Bill Jones was born (1953) and raised in suburban Philadelphia. He received his B.S. degree from MIT in 1975, working with Prof. M. S. Wrighton, and continued his graduate studies of vanadium and molybdenum hydrides with Prof. R. G. Bergman at California Institute of Technology and at the University of California at Berkeley, receiving his Ph.D. from the former in 1979. He spent a year at the University of Wisconsin at Madison as an NSF Postdoctoral Fellow studying η^5–η^1 rearrangements of the cyclopentadienyl ligand with Prof. C. P. Casey, and he joined the faculty at the University of Rochester in 1980, where he began a research program on C–H activation. He is currently a Professor of Chemistry at Rochester and has received Alfred P. Sloan, Camille and Henry Dreyfus, John S. Guggenheim, Fulbright Commission, and Exxon Education Foundation Fellowships.

Frank J. Feher was born in 1958 in Waynesboro, PA. He graduated with his B.S. degree from RPI in 1980 and was the first graduate student to join Jones's group at the University of Rochester, receiving his Ph.D. in 1984 after completing all of the studies in this paper. He undertook one year of postdoctoral study with M. Green at the University of Bristol before taking his current position as an Assistant Professor of Chemistry at the University of California, Irvine, where he now holds a Presidential Young Investigator Award.

Initial observations of oxidative addition to arene C–H bonds in 1965 provided the impetus to look for complexes that would activate the weaker sp^3-hybridized alkane C–H bonds.[3] However, this goal was not achieved until nearly two decades later, encompassing an intermediate period in which much confusion over the thermodynamic feasibility of the reaction took place.[4] In this Account, mechanistic studies with a series of homogeneous rhodium organometallic complexes are summarized that provide for the first time a comparative evaluation of the relative equilibrium constants and rates of reaction for both alkane and arene hydrocarbon activation (eq 1, 2).

Since Chatt observed the first clear example of simple oxidative addition of the C–H bond of naphthalene to

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