5-*Endo* Closure of the 2-Formylbenzoyl Radical[1]

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Abstract: The 5-*endo* cyclization of the 2-formylbenzoyl radical (reaction 2) is shown to be a highly favored process relative to the alternative, 4-*exo-trig* ring closure. This evidence comes from product studies, including ESR and laser flash photolysis studies of transient radical intermediates, from a nitroxide trapping measurement of the rate constant for cyclization of the 2-formylbenzoyl radical, viz., $k_2 = 2 \times 10^8\ \mathrm{s}^{-1}$ at 45 °C, and from the estimated favorable enthalpic change for 5-*endo* cyclization vs 4-*exo-trig* cyclization. It is suggested that rotation of the formyl group in the initially formed conformer of the 2-formylbenzoyl radical may be the rate limiting step in this cyclization.

In 1977, Baldwin[3] provided a concise set of rules for ring closure reactions onto a carbon atom for a reactant containing only first row elements. These rules specify structures for which cyclization onto carbon will be favored and structures for which cyclization will be disfavored. The rules are based on the concept that precise stereoelectronic and steric factors in the reactant determine whether a cyclization will or will not occur. These factors are, however, rather malleable and so exceptions to Baldwin's rules are not uncommon. For example, one disfavored mode is 5-*endo-trig* and several specific attempts by Baldwin et al.[4] to achieve 5-*endo-trig* ring closures were unsuccessful.[5] However, since 1977, a wide variety of heterolytic cyclizations have been discovered which yield the "disfavored" 5-*endo-trig* products.[8-18]

Baldwin's rules apply not only to heterolytic reactions but also to homolytic cyclizations. In the latter area, Beckwith et al.[19] have presented some specific guidelines for radical cyclizations onto an unsaturated carbon atom, i.e., onto sp² or sp hybridized carbon. The disfavored nature of 5-*endo-trig* ring closure for radical cyclizations onto carbon is a matter of general agreement,[20] and Beckwith's first guideline states:[19] "intramolecular addition under kinetic control in lower alkenyl and alkynyl radicals and related species[21] occurs preferentially in the *exo*-mode." Not unnaturally, some exceptions to this guideline have now been discovered.[22]

We have been struck first by the lack of comment and subsequently by the virtual absence of qualitative and complete absence of quantitative data on radical cyclizations onto multiple-bonded, first-row heteroatoms, i.e., onto –N=O and –N=N– and onto the heteroatoms of >C=O, >C=N–, and C≡N. We were particularly intrigued by hints in the literature that 5-*endo* radical cyclizations onto a heteroatom may be *favored* relative to the alternative 4-*exo* cyclization. Thus, Menapace and Kuivila[24] have shown that 2-phenyltetrahydrofuran was formed in the reaction of tri-*n*-butyltin hydride with γ-chlorobutyrophenone, presumably via a 5-*endo* radical cyclization:

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(1) Issued as NRCC No. 37228.

(2) NRCC Research Associate 1987–90.

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(6) Baldwin, J. E.; Kruse, L. I. *J. Chem. Soc., Chem. Commun.* **1977**, 233–235.

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(17) Craig, D.; Smith, A. M. *Tetrahedron Lett.* **1992**, *33*, 695–698.

(18) Alcaide, B.; Plumet, J.; Rodriguez-Campos, I. M.; Garcia-Blanco, S.; Martinez-Carrera, S. *J. Org. Chem.* **1992**, *57*, 2446–2454.

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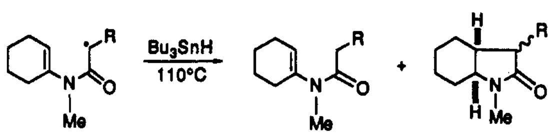
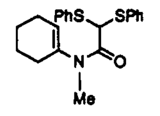
(21) "Related species" applies to ring closure onto the carbon atom of C=O and C≡N groups and onto aromatic groups.[19]

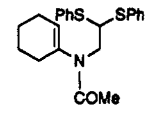
(22) For example,[23] the 5-*endo-trig* cyclizations of the radicals obtained on treating *N*-vinylic-α-halo- and *N*-vinylic-α,α-bis(phenylthio)acetamides with tri-*n*-butyltin hydride, e.g.



(R = H, Me, Ph, SPh)

The sensitivity of this class of radical cyclizations to structure is illustrated by the fact that cyclization does not occur unless the carbonyl group can become incorporated into the five-membered ring.[23] Thus, on treatment with tin hydride, the structure on the left below cyclizes, but the one on the right does not.[23]





(23) Ishibashi, H.; Nakamura, N.; Sato, T.; Takeuchi, M.; Ikeda, M. *Tetrahedron Lett.* **1991**, *32*, 1725–1728. Sato, T.; Machigashira, N.; Ishibashi, H.; Ikeda, M. *Heterocycles* **1992**, *33*, 139–142.

(24) Menapace, L. W.; Kuivila, H. G. *J. Am. Chem. Soc.* **1964**, *86*, 3047–3051.

(25) Cf. the nonradical nature of the reaction of tributyltin hydride with 5-hexenoyl chloride.[26]

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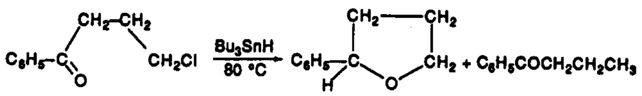
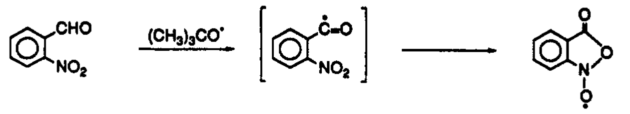


An unequivocal example of a 5-*endo* radical cyclization is provided by Janzen and Oehler's[27] internal spin-trapping of the *o*-nitrobenzoyl radical:



For a number of other 5-*endo* cyclizations purported to involve the addition of carbon-centered radicals to carbonyl oxygen,[28-30] the role of radicals is certainly open to question.[31]

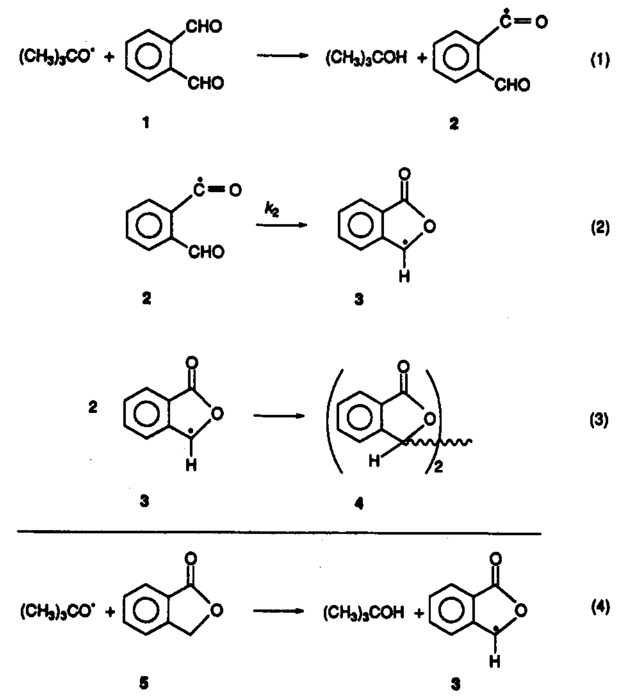
With the above mentioned facts in mind, we decided to examine quantitatively the kinetic behavior of the 2-formylbenzoyl radical (**2**). Like the benzoyl radical,[35a,c] **2** must have its unpaired electron in an sp^2 orbital lying in the plane of the aromatic ring. Thus, we hoped that **2** would prove to be "custom designed" to favor 5-*endo* radical cyclization onto the oxygen atom of the coplanar formyl group (reaction 2 in Scheme 1) and that this reaction would be fast.[37]

The products formed in a very simple experiment (see the Results) demonstrated that reaction 2 occurred. We therefore directed our efforts to measuring the rate of this cyclization and have found it to be extremely rapid ($k_2 = 2 \times 10^8$ s^{-1} at 45 °C).

Results

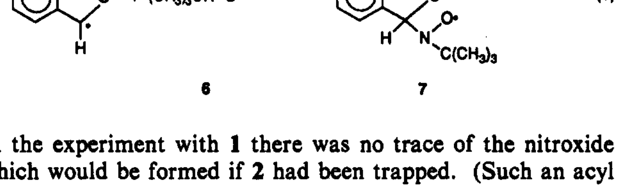
Product Study. Thermal decomposition of di-*tert*-butyl hyponitrite[41] at 59 °C for 24 h in degassed chlorobenzene containing *o*-phthalaldehyde (**1**) yielded a mixture of stereoisomeric 3,3′-biphthalides (**4**). It is obvious that this *radical* reaction must involve a 5-*endo* ring closure of the initial 2-formylbenzoyl radical (**2**) to form the 3-phthalidyl radical (**3**) which then dimerizes, see Scheme 1. The final step in this scheme, reaction 3, had previously been demonstrated via the formation of **4** in a reaction involving the direct generation of **3** by attack of di-*tert*-butyl peroxide derived *tert*-butoxyl radicals on phthalide (**5**) at 135 °C.[42] We have confirmed that **4** is also produced from **5** under hyponitrite conditions.

Scheme 1



Electron Spin Resonance. (i) Direct Studies. Photolysis of mixtures of di-*tert*-butyl peroxide and either *o*-phthalaldehyde (**1**) or phthalide (**5**) in benzene or cyclopropane gave identical ESR spectra: $a^{H}(1H) = 15.7$ G, $a^{H}(1H) = 4.5$ G, $a^{H}(H) = 3.6$ G, $a^{H}(2H) = 1.1$ G, a spectrum which clearly arises from a benzylic radical,[35a,e] i.e., from **3**. The precipitation of **4** on the walls of the ESR tube made it very difficult to record a good spectrum particularly at lower temperatures. Nevertheless, in the experiments where the radicals were generated from **1**, there was no trace of a spectrum which could be assigned to **2**. This absence of **2** allows us to estimate that $k_2 \geq 10^3$ s^{-1} at temperatures in the range –40 to +20 °C.

(ii) Spin-Trapping Studies. Thermolysis of di-*tert*-butyl hyponitrite in the presence of **1** or **5** and 2-methyl-2-nitrosopropane (**6**) in benzene at 25 °C gave the same persistent nitroxide radical **7**: $g = 2.0063$, $a^{N} = 12.84$ G, $a^{H} = 1.05$ G.



In the experiment with **1** there was no trace of the nitroxide which would be formed if **2** had been trapped. (Such an acyl nitroxide would have been easy to identify by its characteristic a^{N} value of *ca.* 7 G[35b,d] and by the absence of splitting by an α-hydrogen atom.)

Rate constants for the trapping of acyl radicals by **6** have not been measured. However, such rate constants are available for

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(26) Lusztyk, J.; Lusztyk, E.; Maillard, B.; Ingold, K. U. *J. Am. Chem. Soc.* **1984**, *106*, 2923–2931.

(27) Janzen, E. G.; Oehler, U. M. *Tetrahedron Lett.* **1983**, *24*, 669–672. For a related 5-*endo* radical cyclization onto an oxygen atom of an NO$_2$ group, see: Janzen, E. G.; Lai, C. C.; Shetty, R. V. *Tetrahedron Lett.* **1980**, *21*, 1201–1204.

(28) Harrison, D. A.; Schwartz, R. N.; Kagan, J. *J. Am. Chem. Soc.* **1970**, *92*, 5793–5795.

(29) Kende, A. S.; Belletire, J. L. *Tetrahedron Lett.* **1972**, 2145–2148.

(30) Praefcke, K. *Tetrahedron Lett.* **1973**, 973–976.

(31) The claimed[28] spectroscopic identification of radical **2** upon photolysis of *o*-phthalaldehyde (**1**) at 77 K is undoubtedly in error,[32] a fact which must cast some doubt on the role of radicals in the cyclizations observed upon photolysis of *o*-phthalate esters,[29] *o*-phthalate thioesters,[30] and related compounds.[30]

(32) Specifically, the carbonyl stretching band of an unstable intermediate found at 2060 cm^{-1}[28] cannot arise from a benzoyl radical (ν = 1828 cm^{-1}),[33] i.e., from **2**, but is almost certainly due to a ketene,[34] i.e., to O═C═C—CH═CH—CH═CH—C═CHOH. Similarly, the species with an ESR *g* value of 2.0036[28] cannot be a benzoyl radical because this *g* value is too large.[35a,c] Indeed, more recent studies[36] have demonstrated that although the photochemistry of *o*-phthalaldehyde is undoubtedly complex there is absolutely no evidence to suggest that it involves the formation of **2**.

(33) Neville, A. G.; Brown, C. E.; Rayner, D. M.; Lusztyk, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1991**, *113*, 1869–1870.

(34) See, for example: Gano, J. E.; Jacob, E. J. *Spectrochim. Acta* **1987**, *43A*, 1023–1025.

(35) (a) Landolt-Börnstein. *Magnetic Properties of Free Radicals* (New Series); Fischer, H.; Hellwege, K. H., Eds.; Springer-Verlag: Berlin, 1977; Vol. 9, Part b. (b) 1979; Vol. 9, Part c.1. (c) 1987; Vol. 17, Part b. (d) 1989; Vol. 17, Parts d.1 and d.2. (e) 1987; Vol. 17, Part c.

(36) Scaiano, J. C.; Encinas, M. V.; George, M. V. *J. Chem. Soc., Perkin, Trans. 2* **1980**, 724–730.

(37) In this connection, we note that the intermolecular analogue of reaction 2 also appears to be a facile process. Under free radical conditions, classical product studies have demonstrated that benzoyl radicals add to benzaldehyde and the adduct radicals then dimerize.[38-40]

$$\mathrm{PhC^{\bullet}O + PhCHO \rightarrow PhC(O)OC^{\bullet}HPh \rightarrow dimer}$$

(38) Rust, F. F.; Seubold, F. H.; Vaughan, W. E. *J. Am. Chem. Soc.* **1948**, *70*, 3258–3259.

(39) Kharasch, M.; Fono, A. *J. Org. Chem.* **1959**, *24*, 606–614.

(40) Protasiewicz, J.; Mendenhall, G. D. *J. Org. Chem.* **1985**, *50*, 3220–3222.

the trapping of primary,[43] secondary,[44] and tertiary[45] alkyl radicals and recent kinetic studies in this laboratory on acyl radicals[33,46] have demonstrated that their reactivity is generally comparable to that of (primary) alkyl radicals. If we assume that this rough kinetic equality extends to reaction with **6**, i.e.,[43] that $k_5 \sim 9 \times 10^6$ M^{-1} s^{-1} at 25 °C, and then make due allowance for the fact that **6** at a nominal concentration of 4.5×10^{-3} M is highly dimerized in solution (K = 1400 M^{-1} at 25 °C, therefore the actual monomeric [**6**] = 1.1×10^{-3} M) and if we further assume that we would have observed the acyl nitroxide if it had been formed at ≥5% [**7**],[47] then we can estimate that $k_2 \geq 2 \times 10^5$ s^{-1} at 25 °C.

Laser Flash Photolysis (LFP). Radical **3** was generated by 308- or 355-nm LFP of a mixture of di-*tert*-butyl peroxide and **5** in benzene at ambient temperature. As expected, a relatively strong absorption at ca. 320 nm, which is a characteristic of benzylic radicals, was observed. The kinetics of the growth of this absorption can be used as a measure of the kinetics of the conversion of **2** to **3** provided that **2** can be generated "instantaneously" when compared to the time scale of the rearrangement. In principle, hydrogen atom abstraction from **1** with *tert*-butoxyl radical[48] should provide a convenient route to **2**, but unfortunately, **1** absorbs relatively strongly both at 308 and 355 nm and undergoes direct photolysis, leading to a previously observed species[36] that possesses a strong absorption in the 350–450-nm region. This absorption was generated, together with that at 320 nm, even upon 355-nm LFP of 70% (v/v) di-*tert*-butyl peroxide:benzene containing as little as 1×10^{-3} M **1**. The resultant overlap of the two absorptions precluded any meaningful kinetic measurements of the growth of **3**. Since at this (and lower) concentration(s) of **1** the pseudo-first-order growth of the absorption at 320 nm due to the formation of **3** might be determined by the rate of reaction 1[48] and not by the rate of reaction 2, further direct attempts to measure the rate of the **2** to **3** rearrangement were abandoned.

Nitroxide Radical Trapping (NRT). Recent work from this laboratory has demonstrated that NRT can be used for, and indeed is the method of choice for, measuring the rates of very fast radical rearrangements[50-53] (fast "radical clocks").[54] The kinetics of reaction 2, which is clearly a very fast cyclization, were therefore examined by the NRT technique[50-53] using 2,2,6,6-tetramethylpiperidine-*N*-oxyl (Tempo) as the trap.

Initial experiments were carried out to measure the rate constant, k_7, for Tempo trapping of the benzoyl radical since, in terms of the trapping reaction of interest (reaction 8, Scheme 2), this is a reasonable model for radical **2**. The benzoyl radical was generated "instantaneously" by 308-nm LFP of pivalophenone (reaction 6, Scheme 2) in *n*-hexane at 23 °C. The experimental rate constant, k_{exptl}, for its pseudo-first-order decay in the presence of Tempo (1.3×10^{-4} to 1.2×10^{-3} M) was measured by monitoring the loss of the benzoyl radical at 1828 cm^{-1},[33,46] using time resolved infrared (TRIR) spectroscopy, eq I. The slope of a plot of k_{exptl}

$$k_{\mathrm{exptl}} = k_0 + k_7[\mathrm{Tempo}] \qquad \text{(I)}$$

vs [Tempo] yielded $k_7 = (1.0 \pm 0.1) \times 10^9$ M^{-1} s^{-1},[46] where the error limits correspond to 2σ. As we would expect,[52] this rate constant is slightly below the diffusion-controlled limit *and* is essentially equal to the rate constant for trapping of the primary *n*-nonyl radical by Tempo, viz.[52,55] $(1.1 \pm 0.1) \times 10^9$ M^{-1} s^{-1} in saturated hydrocarbon solvents of low viscosity.

For the NRT experiment, *tert*-butoxyl radicals were generated by the thermal decomposition of di-*tert*-butyl hyponitrite at 45 °C in the presence of **1** and various concentrations of Tempo in benzene as solvent (see Scheme 2). The solutions were degassed, sealed under vacuum, and heated at 45 °C for ca. 10 half-lives of the hyponitrite.[56] The ratios of the two hydroxylamine products [**9**]/[**8**] were determined by LCMS in the usual way,[50-53] and the results are given in Table 1. The identities of **8** and **9** were confirmed by their mass spectra and by the near constancy of the calculated values of k_2/k_8 (*vide infra* and the final column in

Scheme 2

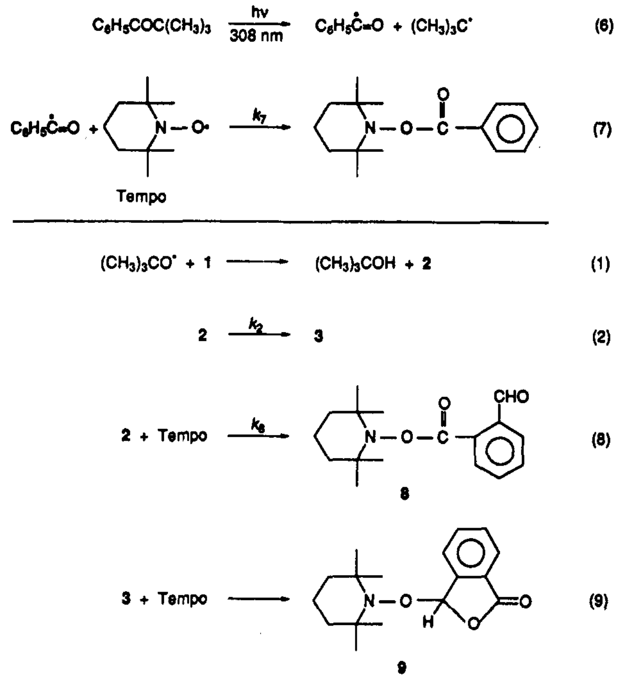

Table 1. NRT Calibration of the **2** → **3** Reaction in Benzene at 45 °C

[hyponitrite]$_0$[a] (mM)	[**1**]$_0$[a] (mM)	[Tempo]$_0$[a] (mM)	[Tempo]$_m$[b] (mM)	[**9**]/[**8**]	[**9**][Tempo]$_m$/[**8**][b] (M) (=k_2/k_8 (M))
28.8	123	481	455	0.950	0.43
28.8	121	360	334	0.909	0.30
14.4	118	224	211	1.59	0.34
14.4	124	175	162	1.78	0.29
7.2	128	78.7	72.2	3.71	0.27

[a] Initial concentration of reagent. [b] [Tempo]$_m$ = [Tempo]$_0$ – 0.9[hyponitrite]; the factor of 0.9 assumes a cage escape efficiency for *tert*-butoxyl of 90%.

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(40) The general experimental procedure which utilizes di-*tert*-hyponitrite as a low-temperature thermal source of *tert*-butoxyl radicals (relative to the thermolysis of di-*tert*-butyl peroxide) in the synthesis of R• dimers via carbon–carbon bond formation in the reaction sequence $(CH_3)_3CO^\bullet + RH \rightarrow (CH_3)_3COH + R^\bullet$, $2R^\bullet \rightarrow R_2$, has been described in an earlier publication.[40]

(41) Huang, H. H. *Aust. J. Chem.* **1976**, *29*, 2415–2422.

(42) Schmid, P.; Ingold, K. U. *J. Am. Chem. Soc.* **1978**, *100*, 2493–2500.

(43) Maeda, Y.; Ingold, K. U. *J. Am. Chem. Soc.* **1979**, *101*, 4975–4981.

(44) Doba, T.; Ichikawa, T.; Yoshida, H. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 3158–3163.

(45) Brown, C. E.; Neville, A. G.; Rayner, D. M.; Ingold, K. U.; Lusztyk, J. To be submitted.

(46) The 5% limit is based on the signal/noise ratio in the ESR spectrum of **7** generated from **1**.

(47) With the assumption that **1** is twice as reactive as benzaldehyde toward *tert*-butoxyl radicals,[49] the pseudo-first-order rate constant for the formation of **2** from 1×10^{-3} M **1** can be calculated to be $2 \times 0.001 \times 6.8 \times 10^7 = 1.36 \times 10^5$ s^{-1}.

(48) Chatgilialoglu, C.; Lunazzi, L.; Macciantelli, D.; Placucci, G. *J. Am. Chem. Soc.* **1984**, *106*, 5252–5256.

(49) Bowry, V. W.; Lusztyk, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1989**, *111*, 1927–1928.

(50) Bowry, V. W.; Lusztyk, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1991**, *113*, 5687–5698.

(51) Beckwith, A. L. J.; Bowry, V. W.; Ingold, K. U. *J. Am. Chem. Soc.* **1992**, *114*, 4983–4992.

(52) Hollis, R.; Hughes, L.; Bowry, V. W.; Ingold, K. W. *J. Org. Chem.* **1992**, *57*, 4284–4287.

(53) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317–323.

(54) Chateauneuf, J.; Lusztyk, J.; Ingold, K. U. *J. Org. Chem.* **1988**, *53*, 1629–1632.

(55) One half-life ~ 7 h at 45 °C.

Table 1) over a 6-fold change in the concentration of Tempo. Additionally, **9** was identified by its independent synthesis in the reaction of **5** with di-*tert*-butyl hyponitrite in the presence of Tempo. Compound **8** was demonstrated to be thermally stable under our reaction conditions by the fact that after complete decomposition of the hyponitrite the [**9**]/[**8**] ratio remained unchanged for a further 40 h at 45 °C. (It should be noted that if **9** is thermally unstable at 45 °C, as might be expected,[53] decomposing to "regenerate" **3** and Tempo, the radical **3** will immediately be retrapped by the excess Tempo to reform **9**, leaving the [**9**]/[**8**] ratio unchanged.)

According to Scheme 2, we can determine the magnitude of the rate constant ratio of interest, k_2/k_8, via eq II:

$$k_2/k_8/\mathrm{M} = ([\mathbf{9}][\mathrm{Tempo}]_\mathrm{m})/[\mathbf{8}] \tag{II}$$

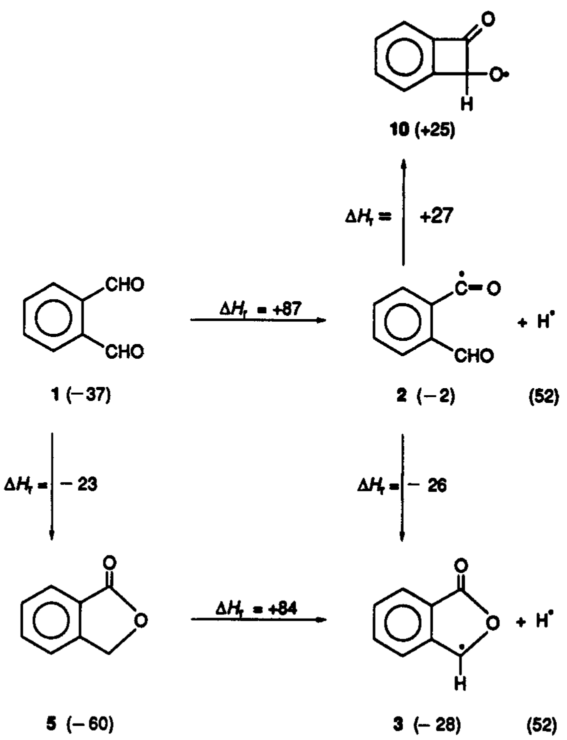
where $[\mathrm{Tempo}]_\mathrm{m}$ is the mean concentration of Tempo in an experiment. However, rate constants for the trapping of carbon-centered radicals by nitroxides are measured at very low nitroxide concentrations whereas NRT experiments are carried out at relatively high nitroxide concentrations. Since trapping rates decline at high nitroxide concentrations,[57] it is necessary to rewrite eq II in the form[51-53]

$$\frac{[\mathbf{9}][\mathrm{Tempo}]_\mathrm{m}}{[\mathbf{8}]} = \left(\frac{k_2}{k_8}\right)_{[\mathrm{Tempo}]\to 0} + a[\mathrm{Tempo}]_\mathrm{m} \tag{III}$$

A plot of the ratio of the yields of the rearranged to unrearranged hydroxylamines multiplied by the mean trap concentration against the mean trap concentration yielded a line with the expected[51-53] positive slope (ca. 0.29) and an intercept $(k_2/k_8)_{[\mathrm{Tempo}]\to 0} \approx 0.25$ M. For this extrapolated rate constant ratio, the appropriate trapping rate constant can be assumed to be equal to k_7 after correction for the change in temperature from 23 to 45 °C and for solvent from hexane to benzene. After applying these minor corrections,[58] we arrive at $(k_7)_{[\mathrm{Tempo}]\sim 0} = 8.0 \times 10^8$ M^{-1} s^{-1}, a value we assume to be equal to $(k_8)_{[\mathrm{Tempo}]\to 0}$. By combining this rate constant with the extrapolated rate constant ratio of 0.25 M, we arrive at $k_2 = 2.0 \times 10^8$ s^{-1} at 45 °C.

Thermochemical Calculations. Although experimental thermochemical data on **1** and **5** are incomplete, we have been able to estimate the enthalpic relationships shown in Scheme 3 by the method of group additivity[59] and the calculated (gas-phase) heats of formation, $\Delta H_f°$ (kcal/mol). The heats of formation of radicals **2** and **3** are likewise unknown. They have been estimated by assuming that the aldehydic C–H bond strength in **1** is the same as that in benzaldehyde (87 kcal/mol)[60,61] and that the strength of the benzylic C–H bond in **5** is the same as that in ethylbenzene[63] (84 kcal/mol). The heat of formation of the 4-*exo-trig* cyclization product **10** has also been estimated by the group additivity method using certain assumptions.[65]

Scheme 3[a]

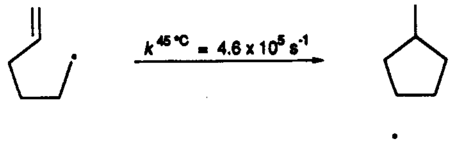


[a] Units are kcal/mol.

Despite the fact that there are many assumptions involved in determining the enthalpy changes shown in Scheme 3, there can be no doubt that thermochemistry predicts that the 5-endo cyclization of **2** to **3** is a strongly exothermic reaction (−26 kcal/mol) whereas the 4-*exo-trig* cyclization of **2** to **10** is strongly endothermic (~+27 kcal/mol). The 5-*endo* cyclization of **2** would therefore appear to be favored not only by stereoelectronic but also by enthalpic factors.

Discussion

We have unequivocally demonstrated that the 5-*endo* cyclization, **2** → **3**, which involves only first row elements is a highly favored process relative to the alternative, 4-*exo-trig* ring closure, **2** → **10**. Our evidence comes from product studies, including ESR and LFP studies of transient radical products, from the measurement of the rate constant for cyclization of **2**, viz., $k_2 = 2 \times 10^8$ s^{-1} at 45 °C, and from the estimated favorable enthalpic change for the 5-*endo* cyclization vs the 4-*exo-trig* cyclization. With regard to the large magnitude of the rate constant for reaction 2, we note that this cyclization is some 400 times faster than the famous favored[3] 5-*exo-trig* cyclization of the 5-hexenyl radical,[66] reaction 10 and about 1000 times faster than the analogous favored cyclization of the corresponding acyl radical,[46] reaction 11. Of course, four C–C bond rotations must be "frozen" in the transition states for reactions 10 and 11 so that entropic



(10)

(11)

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(57) Because high nitroxide concentrations cause an increase in the overall polarity of the solvent.[52] The change of the trapping rate constants by Tempo with the change of its concentration and polarity of the solvent is an inherent problem of the NRT method. However, with careful attention to detail,[52] it is relatively easy to introduce the necessary corrections (*vide infra*).

(58) Temperature: activation energy = 1.8 ± 0.9 kcal/mol,[55] therefore increased k_7 by a factor of 1.2. Solvent: for nonyl radical trapping in benzene at 18 °C, $k = 6.7 \times 10^8$ M^{-1} s^{-1} [52] vs *ca.* 1.1×10^9 M^{-1} s^{-1} in a low viscosity alkane,[52,55] therefore decreased k_7 by a factor of 0.61. Overall correction factor ≈ 1.2 × 0.61 ≈ 0.73, i.e., $k_7 = 0.73 \times 1.1 \times 10^9 = 8.0 \times 10^8$ M^{-1} s^{-1} in benzene at 45 °C.

(59) Benson, S. W. *Thermochemical Kinetics*, 2nd ed.; Wiley-Interscience: New York, 1976.

(60) Solly, R. K.; Benson, S. W. *J. Am. Chem. Soc.* **1971**, *93*, 1592–1595.

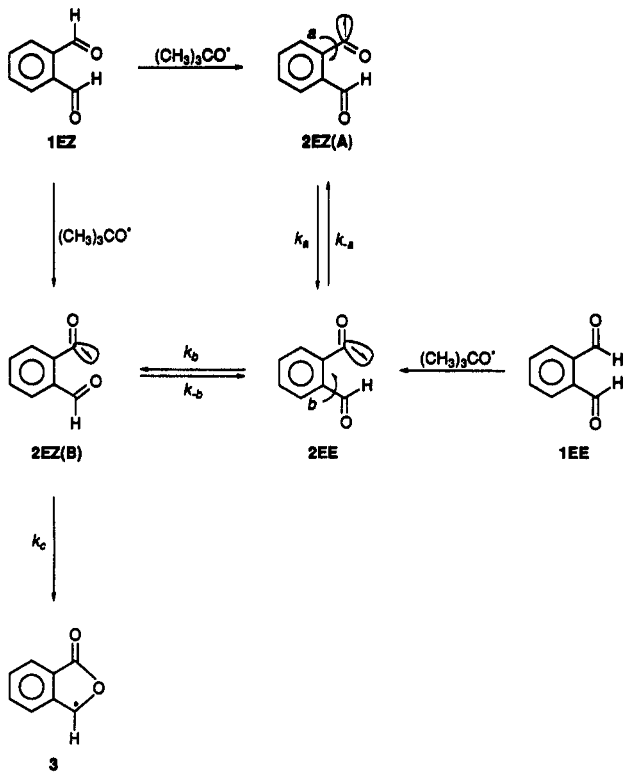
(61) Since both RC•=O and ArC•=O are σ radicals the aldehydic C–H bond strengths in RCHO and ArCHO are essentially identical and do not depend on the nature or R or Ar. (See ref 62 for some RC(O)–H bond strengths.)

(62) Griller, D.; Kanabus-Kaminska, J. M.; Maccoll, A. *THEOCHEM* **1988**, *40*, 125–131.

(63) This choice was made because an ester group appears to provide no stabilization to a neighboring radical center, e.g., $D[\mathrm{C_6H_5CO_2CH_2{-}H}] \sim$ 100 kcal/mol[64] and $D[\mathrm{CH_3CH_2{-}H}] \sim$ 100 kcal/mol.[62] The bond strength chosen for ethylbenzene is based on $D[\mathrm{C_6H_5CH_2{-}H}] \sim$ 88 kcal/mol[62] and $D[\mathrm{CH_3CH_2{-}H}] - D[\mathrm{(CH_3)_2CH{-}H}] \sim$ 4 kcal/mol.[62]

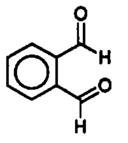
(64) Solly, R. K.; Benson, S. W. *Int. J. Chem. Kinet.* **1971**, *3*, 509–522.

Scheme 4

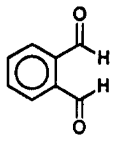


factors strongly disfavor these two ring closures. In contrast, entropic factors are much less important for reaction 2 (*vide infra*).

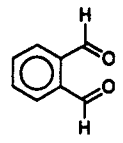
o-Phthalaldehyde can exist in three different conformations, of which **1ZZ** is probably disfavored because of steric repulsion between the two oxygen atoms. The **1EE** conformation is also likely to be somewhat disfavored because of (peri-) repulsion of the oxygen atoms by the aromatic hydrogens at positions 3 and 6.[67] Thus, it seems likely that **1EZ** is the main conformer, but since some of the **1EE** conformer will also be present, we represent the overall ring closure of **2** to **3** by the sequence of reactions shown in Scheme 4.



1EZ



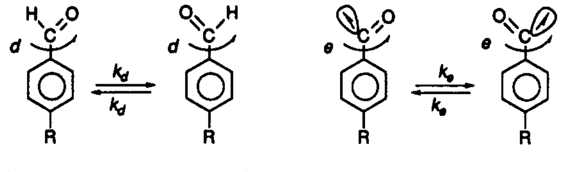
1EE



1ZZ

Three conformers of the *o*-formylbenzoyl radical may be formed in the initial hydrogen abstraction step (see Scheme 4). Of these three only the **2EZ(B)** conformer can undergo cyclization to form **3**. This reactive conformer may be formed directly or indirectly. The direct route involves H-atom abstraction from the *E*-CH bond of **1EZ**. There are two indirect routes to **2EZ(B)**. One involves an initial H-atom abstraction from the *Z*-CH bond of **1EZ** to produce **2EZ(A)** followed by the C–C bond rotation, a (where a may be an inversion rather than a rotation) to form the **2EE** conformer, this being followed by a second C–C bond rotation, b, to yield **2EZ(B)**. The second indirect route to **2EZ(B)** involves hydrogen abstraction from the **1EE** *o*-phthalaldehyde conformer to yield **2EE** followed by the C–C bond rotation b.

It seems highly probable that the rate of rotation/inversion of bond a is much greater than the rate of rotation of bond b (i.e., $k_a \gg k_b$) because there is a fairly substantial barrier to formyl group rotation in aromatic aldehydes[68] relative to the much more facile rotation/inversion of the C•═O moiety in aroyl radicals.[69,70] In the (understandable) absence of information on the rotation barrier for the formyl group in **1** and **2** and on the rotation/inversion barrier for the C•═O moiety in **2**, we will make the assumption that the difference in enthalpic barriers for these two processes, $\Delta H_b^{\ddagger} - \Delta H_a^{\ddagger}$, will have the same magnitude as that found by Grossi and Placucci[69] for the rotational free energy difference between *p*-substituted benzaldehydes and the corresponding benzoyl radicals, $\Delta G_d^{\ddagger} - \Delta G_e^{\ddagger} = 4.8$–$5.0$ kcal/mol (mean 4.9 kcal/mol):



(R = H, CH$_3$, OCH$_3$, N(CH$_3$)$_2$)[69]

That is, we will assume that $\Delta H_b^{\ddagger} - \Delta H_a^{\ddagger} = 4.9$ kcal/mol. We will also assume that $\Delta H_b^{\ddagger}$ has the same magnitude as $\Delta G_d^{\ddagger}$ for terephthalaldehyde (R = CHO), *viz.*[68] 6.9 kcal/mol.[71] This second assumption may underestimate $\Delta H_b^{\ddagger}$ slightly because the **2EE** conformer may be slightly more stable than **2EZ(B)** for steric reasons whereas, for the degenerate rotation d, the two conformers are unhindered (and have equal energy). That is, k_b may be slightly greater than k_d for terephthalaldehyde.

By ignoring any small entropy changes in the asymmetric bond rotations, a and b, and making the two assumptions described above, we can estimate that at 45 °C

$$k_a = (ekT/h)\exp(-2000/RT) = 6.4 \times 10^{11}\ \mathrm{s}^{-1}$$

and

$$k_b = (ekT/h)\exp(-6900/RT) = 3.3 \times 10^{8}\ \mathrm{s}^{-1}$$

Thus, in the conversion of **2EZ(A)** into the reactive **2EZ(B)** conformer, the rotation/inversion step a is certainly not rate limiting. More interestingly, the C–C bond rotation step b which converts **2EE** into the reactive conformer is estimated to have a rate constant k_b (3.3×10^8 s^{-1}), which is not sensibly different from the experimentally measured rate constant for ring closure k_2 (2.0×10^8 s^{-1}). It is therefore possible that the overall cyclization reaction might have two kinetically distinct regions. That is, if $k_b \ll k_c$, an initial, fast, formation of **3** would correspond to the cyclization of that fraction of the overall H-atom abstraction process which yielded the **2EZ(B)** conformer directly. This would

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(65) For **10H** (the alcohol derived from **10**), we took the usual values[59] of ΔH_f° for the groups HC$_B$(H), CO(C$_B$)(C), C$_B$(CO), C$_B$(C), and O(C)(H). We then assumed that the group C(H)(C$_B$)(CO)(O) could be approximated by the C(H)(C$_2$)(CO) group and that the ring strain could be equated to that for cyclobutene (29.8 kcal/mol)[59] minus the difference in ring strain between cyclobutane and cyclobutanone, viz.,[59] 26.2–22.6 = 3.6 kcal/mol, i.e., strain in **10H** = 29.8–3.6 = 26.2 kcal/mol. To obtain ΔH_f° for **10**, we then took the usual values for D[O–H] for alcohols (104 kcal/mol) and ΔH_f[H•] (52 kcal/mol) giving ΔH_f°(**10**) = +24.6 kcal/mol.

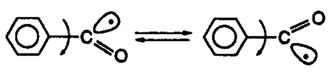
(66) Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 7739–7742.

(67) LFP of **1** yields two triplet species with lifetimes of 6 and 36 ns, which Scaiano et al.[36] have assigned to **1EZ*** and **1EE***, respectively, on the grounds that **1EE*** must undergo bond rotation prior to intramolecular hydrogen transfer from carbon to oxygen.

(68) Drakenberg, T.; Sommer, J.; Jost, R. *J. Chem. Soc., Perkin Trans. 2* **1980**, 363–369.

(69) Grossi, L.; Placucci, G. *J. Chem. Soc., Chem. Commun.* **1985**, 943–944.

(70) Possibly because in a *rotational* process

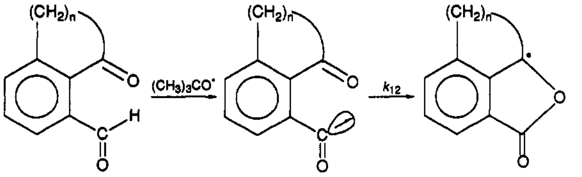


the unpaired electron can become delocalized into the aromatic ring in the perpendicular transition state.[69]

(71) Relevant data (e.g., appropriate substituent parameters for an *o*-formyl group) which would allow a more precise calculation are unavailable.

be followed by a slower process for which rotation about bond b became the rate controlling step for cyclization. Unfortunately, even if there are, in fact, two quite distinct kinetic regions, it is not possible with present day kinetic techniques to assess even their relative contributions to the overall process, i.e., the ratio $[\mathbf{2EZ(B)}]_{\text{initial}}/([\mathbf{2EZ(A)}]_{\text{initial}} + [\mathbf{2EE}]_{\text{initial}})$, let alone the absolute magnitude of k_c and k_b.

To summarize, if the direct formation of the reactive **2EZ(B)** conformer is comparatively unimportant relative to its indirect formation via **2EE**, then *it is quite possible that step b (Scheme 4) is rate limiting for a large portion of this 5-endo ring closure.* Thus, not only has our work demonstrated the facility with which a 5-*endo* cyclization onto carbonyl oxygen *can* occur when a radical has an appropriate stereoelectronic architecture but also it raises the intriguing possibility that the "conformationally preorganized" cyclization shown in general terms in reaction 12 may be noticeably faster than reaction 2. Experiments to determine the magnitude of k_{12} and the rate constants for other 5-*endo* radical cyclizations onto carbonyl oxygen will be undertaken shortly.



(12)

Experimental Section

Materials. *o*-Phthalaldehyde (**1**) (Aldrich), phthalide (**5**) (Aldrich), and Tempo (Aldrich) were recrystallized from hexane, 95% ethanol, and heptane, respectively. Di-*tert*-butyl peroxide (Aldrich) and pivalophenone (Aldrich) were purified by passage through alumina. 2-Methyl-2-nitrosopropane (**6**) (Aldrich) was recrystallized from methanol at −16 °C. Di-*tert*-butyl hyponitrite was prepared as described previously.[72]

3,3′-Biphthalide (**4**) was synthesized from phthalide (**5**) and from *o*-phthalaldehyde (**1**). Thus, **5** (5.23 g, 39 mmol) and di-*tert*-butyl hyponitrite (1.69 g, 9.7 mmol) in 20 mL of chlorobenzene were heated at 52 °C for 18 h; a white solid was removed by filtration and extracted with 200 mL of ether (in portions). Removal of the ether and recrystallization from acetic acid gave 0.28 g of a white solid, mp 268–274 °C. The ether-insoluble portion was also recrystallized from acetic acid to give 21 mg of white solid, mp 262–264 °C. The two solid products showed identical ^{1}H NMR spectra (CF_3COOH, TMS) except for differences in the relative heights of singlets at δ 6.0 and 6.3, the former being larger in the ether-insoluble fraction and *vice versa* for the ether-soluble fraction. Alternatively, **5** (5.36 g, 40 mmol) and di-*tert*-butyl hyponitrite (1.39 g, 8.0 mmol) in 20 mL of benzene were heated at 80 °C for 0.5 h, giving a white precipitate of mixed biphthalides on cooling to 5 °C. The precipitate was removed by filtration, washed with a small amount of benzene, and dried, yielding 0.59 g of solid, mp 247–265 °C (31% yield corrected for hyponitrite decomposition cage effect). Huang[42] and Molho and Aknin[73] have previously reported fractional crystallization of **4** into *meso* (lit. mp 260–262 °C[42] and 260 °C[73]) and racemic (lit. mp 293–295 °C[42] and 290 °C[73]) isomers. An intense IR band at 1780 cm^{-1} confirms that **4** is a lactone.

Similarly, **1** (1.53 g, 11.4 mmol) and di-*tert*-butyl hyponitrite (0.498 g, 2.86 mmol) in 5.5 mL of chlorobenzene were heated at 59 °C for 24 h; filtration of the white solid and washing with a little chloroform yielded 0.52 g (66%) of a 1:1 mixture of racemic and *meso*-biphthalide (mp 266–270 °C).

3-(2′,2′,6′,6′-Tetramethyl-1′-piperidineoxyl)phthalide (9). A mixture of phthalide (0.50 g, 3.73 mmol), di-*tert*-butyl hyponitrite (0.36 g, 2.08 mmol), and Tempo was dissolved in a minimal (0.9 mL) amount of benzene in a small test tube. The contents of the tube were flushed with nitrogen, stoppered with a septum, pierced with a needle for pressure release, and placed in a water bath at 50 °C for 2 days, following which the solution was concentrated under reduced pressure to give a red gum which crystallized upon addition of hexane. Two crops of sticky brown crystals were obtained (total 0.40 g) and were shown to be phthalide by mixed mp with authentic material. The mother liquors were concentrated to a red oil that was subjected to chromatography on silica gel (Merck, grade 60). Elution with hexane and then 1:1 hexane:ether gave, after removal of solvent, unchanged Tempo (red oil, 0.08 g, identified by odor, color, and comparison of IR spectra), followed by several intermediate fractions, one of which gave yellow crystals that became white after washing with hexane: 0.08 g (37% based on unrecovered phthalide), mp 103–105 °C. IR (mineral oil): 1775, 1750, 1380, 1348, 1255, 1250, 1202, 1140, 1050 cm^{-1}. The ^{1}H-NMR spectrum ($CDCl_3$) showed signals at δ 1.04 (s, 3H), 1.24 (s, 3H), 1.36 (s, 3H), 1.43 (s, 3H), 1.58 (s(br), 6H), 6.69 (s, 1H), 7.5–7.9 (m, 4H). The $CDCl_3$ solution was allowed to evaporate in an air stream, giving white crystals, mp 104–105 °C. Exact mass (CI-NH_3): calcd M + H$^+$ 290.1756; obsd 290.1755. Mass spectrum (CI-CH_4): *m/e* (relative abundance) 291 (0.4), 290 (2.3), 274 (1.4), 174 (1.4), 166 (1.1), 157 (3.3), 156 (28, Tempo$^+$), 146 (6.4), 141 (10), 140 (100), 134 (0.7), 133 (4); (EI) 157 (6.3), 156 (60), 140 (7), 138 (15), 134 (11), 133 (100, $C_8H_5O_2^+$), 123 (23), 105 (8), 77 (3.6), 69 (3.1).

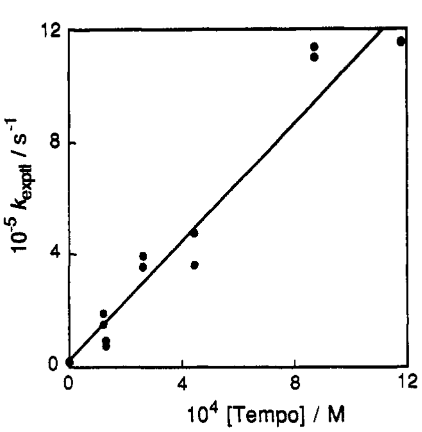


Figure 1. Plot of k_{exptl} as a function of Tempo concentration.

Our attempt to isolate **8** by similar means from the di-*tert*-butyl hyponitrite initiated reaction of **1** with Tempo was unsuccessful.

Kinetics and Instrumentation. The 308- and 355-nm LFP[74] and (308 nm) TRIR equipment[33,46,75] have been described previously, as have the relevant experimental procedures. The details of the TRIR LFP measurement of the rate constant, k_7, for Tempo trapping of the benzoyl radical were as follows. The benzoyl radical was generated "instantaneously" by 308-nm LFP of an argon-saturated, 0.017 M solution of pivalophenone in *n*-hexane, flowing through a 2-mm CaF_2 IR cell. The time evolution of the radical's concentration was followed by monitoring its C═O stretching absorption at 1828 cm^{-1}. This absorption decayed with second-order kinetics in the absence of Tempo, but the decay was converted to pseudo-first-order kinetics upon the addition of sufficient Tempo. The concentration of Tempo was varied from 1.3×10^{-4} to 1.2×10^{-3} M, and the resulting decay traces were fitted with mixed first- and second-order kinetics (using for the latter the $2k_t/\epsilon$ value derived from the analysis of the decay of the benzoyl radical in the absence of Tempo) to obtain the experimental rate constants, k_{exptl}, for the pseudo-first-order decays of the benzoyl radical. A plot of k_{exptl} vs [Tempo], Figure 1, produced a straight line, the slope of which, in accordance with eq I (*vide supra*), gave $k_7 = (1.0 \pm 0.1) \times 10^9$ M^{-1} s^{-1}.

The trapping experiments with Tempo were carried out in 2 mL of degassed benzene with *ca.* 0.12 M **1** and various concentrations of di-*tert*-butyl hyponitrite and Tempo (see Table 1). Samples were heated at 45 °C until the hyponitrite had decomposed completely (ca. 10 half-lives) and were then stored at −10 °C until analysis with a Varian TS88 thermospray LCMS using a 5-μm reversed-phase column and eluting with 30% aqueous acetonitrile containing 5×10^{-3} M ammonium acetate at a flow rate of 1 mL/min. The Tempo-trapped products, **8** and **9** (Scheme 2), were eluted after 6.7 and 7.7 min, respectively. The ratios of the two products [**9**]/[**8**] were determined by LCMS in the usual way[50–53] from the ratio of the total ion counts with the assumption that both products are ionized either totally or to the same degree in the mass spectrometer. The identity of **9** was confirmed by independent synthesis,

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[72] Mendenhall, G. D. *Tetrahedron Lett.* **1983**, *24*, 451–452.

[73] Molho, D.; Aknin, J. *Bull. Soc. Chim. Fr.* **1965**, 3021–3024.

[74] Kazanis, S.; Azarani, A.; Johnston, L. J. *J. Phys. Chem.* **1991**, *95*, 4430–4435.

[75] Rayner, D. M.; Nazran, A. S.; Drouin, M.; Hackett, P. A. *J. Phys. Chem.* **1986**, *90*, 2882–2888. Ishikawa, Y.; Hackett, P. A.; Rayner, D. M. *J. Am. Chem. Soc.* **1987**, *109*, 6644–6650.

and that of **8** was confirmed by its mass spectrum and by the expected trend in the [**9**]/[**8**] ratio over a 6-fold change in the concentration of Tempo (see Table 1). The thermal stability of adduct **8** was tested by allowing one of the postreaction mixtures for which the [**9**]/[**8**] ratio had been established to remain for a further 40 h at 45 °C and then remeasuring the [**9**]/[**8**] ratio. The two ratios were identical within the experimental error.

ESR spectra were recorded on a Varian E104 EPR spectrometer. LC–MS analyses were performed with an HP 1090 liquid chromatograph equipped with an HP ODS hypersil (5 μm) 200- × 2.1-mm column, thermospray interfaced to an HP 5988 mass spectrometer. Exact masses were obtained on a VG Analytical model VG7250S instrument by Mr. James Windak at the University of Michigan. Conventional mass spectra were obtained with an HP 5985B GC–MS by direct probe insertion. Nuclear magnetic resonance spectra were recorded using a Varian XL-200 instrument.

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