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The Reaction of Diphenylcarbene with Nitroxides[1]

H. L. Casal, N. H. Werstiuk,[2] and J. C. Scaiano*

Division of Chemistry, National Research Council of Canada, Ottawa, Ontario, Canada K1A 0R6

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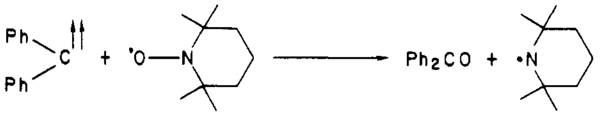
Diphenylcarbene reacts with 2,2,6,6-tetramethylpiperidine *N*-oxide with a rate constant of 2.7×10^8 M^{-1} s^{-1} in acetonitrile at room temperature. The reaction involves the transfer of an oxygen atom, leading to benzophenone and 2,2,6,6-tetramethylpiperidinyl radical in essentially quantitative yields. In the case of 4-hydroxy-2,2,6,6-tetramethylpiperidine *N*-oxide insertion at the O–H bond competes with reaction at the nitroxide center, with rate constants of 1.9×10^7 and 2.8×10^8 M^{-1} s^{-1}, respectively. The reaction at the OH site is not enhanced significantly by the presence of a paramagnetic center in the molecule.

During the last few years, carbenes have been the subject of numerous studies using laser flash photolysis techniques.[3-5] In particular, diphenylcarbene has been the object of much attention and controversy.[6-9]

Diphenylcarbene can be readily generated by photodecomposition of diphenyldiazomethane;[3] it has a ground-state triplet which in laser photolysis experiments shows a characteristic absorption at ca. 315 nm.[9] Olefins, alcohols, hydrogen donors, and oxygen all quench this absorption.[10] A rather interesting possibility, that has not been examined before, is the abstraction of oxygen atoms by carbenes. For example, the reaction of triplet diphenylcarbene with a persistent nitroxide such as 2,2,6,6-tetramethylpiperidine *N*-oxide (Tempo) would be spin allowed *and* over 100 kcal/mol exothermic, reaction 1.

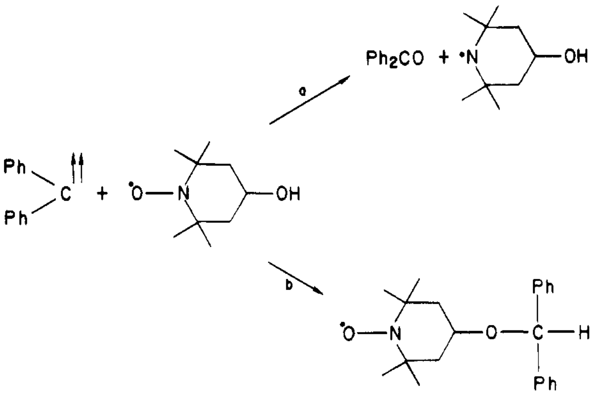


(1)

Reaction 1 has a few parallels in free radical chemistry, such as the reaction of *tert*-butoxyl carbon monoxide[11] (to yield CO_2) or with phosphorus(III) substrates[12] (to yield P(V) products). A few examples involving peroxy radicals are also known.[13] Recently, the reaction of ethynyl radicals with molecular oxygen was examined.[14]

While the reaction of diphenylcarbene (and other carbenes) with molecular oxygen to yield benzophenone has been recognized for many years,[15] its mechanism is believed to involve the carbonyl oxide, Ph_2COO, which subsequently reacts to yield benzophenone and its diperoxide.[16] The carbonyl oxide has been recently characterized with laser flash photolysis.[17]

Another reason for our interest in the reaction with nitroxides is related to the possible competition of two reaction paths in the case of substrates such as 4-hydroxy-Tempo, reaction 2.



(2)

The question of singlet vs. triplet pathways in the reaction of diphenylcarbene with hydroxylic substrates has been the subject of considerable controversy in the last few years.[3,18,19] Reaction 2a could in principle be spin allowed, provided that there is sufficient interaction for the nitroxide center to act as a "spin catalyst" for attack at the OH position. It thus seemed an interesting new avenue to address the importance of spin factors in determining carbene reactivities, even if the EPR data suggest that the interaction between the two positions is weak.[20]

The present study deals with the reaction of diphenylcarbene with Tempo, 4-hydroxy-Tempo, and 4-amino-Tempo. Kinetic and spectroscopic studies with laser flash techniques have been confirmed with product studies; in addition, we have briefly examined the photochemistry of Tempo and its derivatives in various solvents. While these reactions are not the main subject of this report, some nitroxide photodecomposition is usually unavoidable and it is important to establish if these photoreactions can affect the outcome of studies of the diphenylcarbene-nitroxide reactions.

Results

All experiments were carried out under oxygen-free conditions. Special care was taken to ensure that laser and

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(1) Issued as NRCC-23637.

(2) NRCC Visiting Scientist. Permanent address: Department of Chemistry, McMaster University, Hamilton, Ontario.

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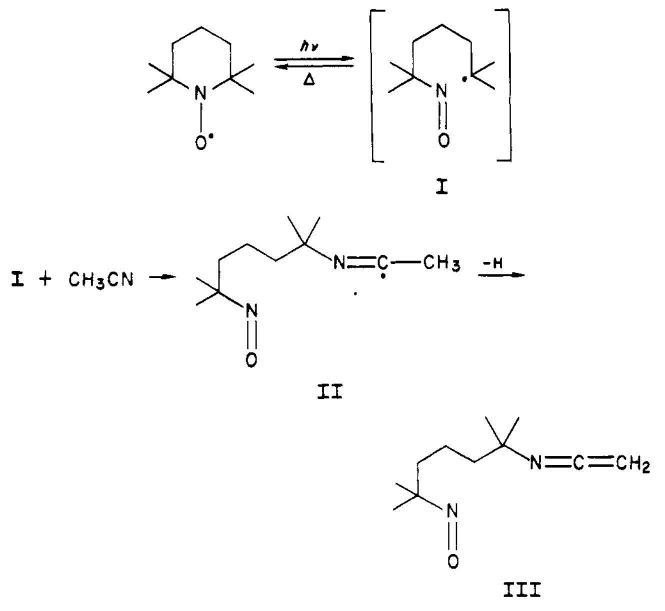
Scheme I



product studies were performed under comparable conditions, especially with regard to the diphenyldiazomethane (DPDM) concentration, since some dependence of the product ratios on this is common.[21]

(1) Product Studies. (a) Control Experiments in the Absence of DPDM. The spectroscopic characteristics of DPDM and Tempo and its derivatives are such that some direct photodecomposition of Tempo is unavoidable, particularly because the kinetic parameters (vide infra) are such that the Tempo concentration required is usually ca. two orders of magnitude higher than the DPDM concentrations.

Most of our experiments were carried out in acetonitrile, where direct photolysis of Tempo yields a single addition product, possibly by the mechansim of Scheme I. This is confirmed by using CD_3CN as the solvent, GC/MS analysis shows an increase of two units in M^+. The mechanism of the II → III transformation is not clear at this point, although it may involve a second molecule of Tempo; the structure of III should be regarded as only a tentative assignment. Alternatively, an isomer of III can result if Tempo traps $\dot{C}H_2CN$ formed by H abstraction by excited Tempo. The same reaction pattern was observed for the other Tempo derivatives in acetonitrile solvent (see Experimental Section). Only 1% yield of ring opened products was obtained in the time required ($\sim$7 min) for the quantitative decomposition of 10^{-4} M DPDM.

In the case of isooctane as solvent, Tempo also seems to add to the solvent with loss of one hydrogen atom. We presume that the reaction involves the attack of isooctane by I or the tetramethylpiperidyl radical, followed by the trapping of the alkyl radical.

The direct photodecomposition of Tempo and its derivatives clearly deserves more detailed study, and some reports on the subject have appeared in the literature.[22] The point of our direct photolysis experiments was to be able to ensure that the products of this reaction would not interfere with the study of the reactions of diphenylcarbene and the nitroxides. Additional details are given in the Experimental Section.

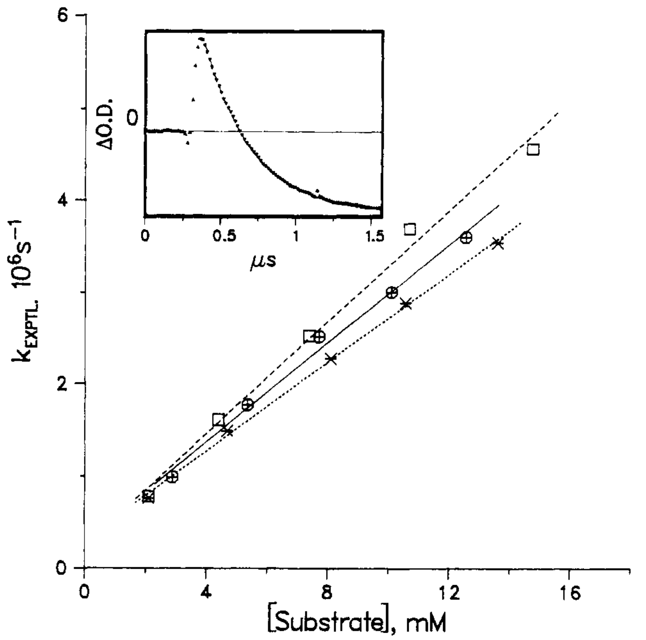
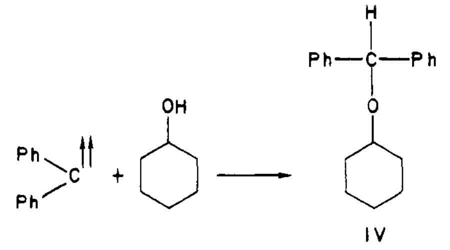


Figure 1. Plot of k_{exptl} measured at 300 K for the quenching of triplet diphenylcarbene in acetonitrile solution: (–) substrate = Tempo; (– –) substrate = 4-hydroxy-Tempo; (··) substrate = 4-amino-Tempo.

(b) Reaction of Diphenylcarbene with Nitroxides. The photolysis of DPDM (typically $\sim 10^{-4}$ M) in acetonitrile at room temperature, in the presence of sufficient Tempo to trap >90% of the carbene (as determined by laser photolysis), yields benzophenone in >90% yield and tetramethylpiperidine in equimolar amounts. The products are thus consistent with reaction 1 as the only mode of carbene decay. Further, the tetramethylpiperidinyl radical decays, as expected, by reaction with the solvent in what we presume to be a very slow reaction. Consistent with earlier studies, no dimerization products were observed.[23]

In the case of cyclohexanol, used as a reference substrate for 4-hydroxy-Tempo, the reaction with diphenylcarbene gives over 90% yield of the expected ether (IV), reaction 3.



(3)

In the case of 4-hydroxy-Tempo we found products from reactions paths 2a and 2b. The benzophenone-to-ether ratio was ca. 16 for a 0.0015 M solution of 4-hydroxy-Tempo indicating that attack at the nitroxide center predominates even though it is more hindered than the OH group. Benzophenone and the corresponding amine accounted for ca. 90% yield based on DPDM.

In the case of 4-amino-Tempo attack at the nitroxide group was the only detectable reaction path. We estimate insertion at the N–H bond to account for less than 2% of the overall reaction. No indication of attack at the C–H bond α to NH_2 could be obtained, even if this position can be expected to be highly reactive.

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Table I. Kinetics of the Reactions of Diphenylcarbene at Room Temperature

substrate	solvent	kq^{a}	$k_{NO}{}^{a,b}$	$k_{insertion}{}^{a,c}$
cyclohexanol	isooctane	$(6.3 \pm 0.3) \times 10^6$		6.3×10^6
	chlorobenzene	$(2.2 \pm 0.1) \times 10^7$		2.2×10^7
	acetonitrile	$(1.3 \pm 0.1) \times 10^7$		1.3×10^7
Tempo	isooctane	$(7.3 \pm 0.1) \times 10^8$	7.3×10^8	
	acetonitrile	$(2.7 \pm 0.1) \times 10^8$	2.7×10^8	
4-hydroxy-Tempo	chlorobenzene	$(1.7 \pm 0.1) \times 10^8$		
	acetonitrile	$(3.0 \pm 0.2) \times 10^8$	2.8×10^8	1.9×10^7
4-amino-Tempo	isooctane	$(4.8 \pm 0.3) \times 10^8$		
	acetonitrile	$(2.4 \pm 0.1) \times 10^8$	2.4×10^8	$<5 \times 10^6$

[a] In units of M^{-1} s^{-1}. [b] Attack at the nitroxide center, assuming the ratio of rate constants can be extracted from the product studies. [c] Attack at O–H or N–H, as applicable.

(2) Laser Flash Photolysis Studies. All experiments were carried out with 308-nm pulses (~4 ns, less than 80 mJ/pulse), and a flow system to prevent substrate depletion and product excitation. The carbene was readily detectable at 315 nm and in the presence of scavenger its decay followed clean first-order kinetics, leading to bleaching which reflects the consumption of the parent diazo compound (see insert in Figure 1). Plots of the pseudo-first-order rate constant for carbene decay, as a function of substrate concentration lead to the bimolecular rate constants for carbene scavenging by the various quenchers. Representative plots are illustrated in Figure 1 and our results are summarized in Table I.

The overall rate constant k_q for the reaction of diphenylcarbene with Tempo and derivatives is well below the diffusion limit. The values of k_q are practically the same for reaction with Tempo, 4-OH-Tempo, and 4-amino-Tempo in acetonitrile while there is a marked difference between k_q for Tempo and 4-amino-Tempo when the solvent is isooctane.

The reaction of diphenylcarbene with cyclohexanol is slower by more than an order of magnitude than the reaction with Tempo derivatives, but comparable with other reactions with alcohols.[19] The reaction with 4-hydroxy-Tempo could not be measured in isooctane due to lack of solubility of this substrate in isooctane.

On the basis of the product ratios the overall reaction rate constant k_q can be partitioned according to the two sites of attack; the nitroxide center (k_{NO}) and the OH or NH_2 ($k_{insertion}$). The results of this partition are included in Table I. It should be noted that this treatment of the rates assumes that no carbene singlet quenching occurs prior to equilibration with the triplet. This assumption is important only where a competition actually takes place, as in the case of 4-hydroxy-Tempo. The concentration of 4-hydroxy-Tempo used in the product studies was 0.0015 M, and since $k_{isc} = 3 \times 10^9$ s^{-1}, for diphenylcarbene,[7,24] less than 1% of the singlet would be trapped before intersystem crossing assuming the rate constant for singlet trapping to be 10^{10} M^{-1} s^{-1}.

We could not detect a discrete reaction intermediate (ylide ?) in the reaction of diphenylcarbene with Tempo. Weak absorptions were observed in the 350–400-nm region, but it was not possible to characterize them in any detail.

Discussion

The reaction of diphenylcarbene with Tempo (see reaction 1) provides a rather unique example in carbene chemistry. Other documented examples of oxygen transfer, such as carbon monoxide[11] and P(III) compounds also involve systems where the valency of the central atom can increase by two units. Only in the case of phosphorous compounds has the intermediate (a phosphoranyl radical in this case) been detected,[12] although a trioxide intermediate is probably involved in the oxygen exchange reaction between peroxy and alkoxy radicals.[13]

In the case of reaction 1 we expect one third of the encounters to have the appropriate spin configuration for reaction. The process is, while fast (see Table I), well below the diffusion limit.

The reaction with 4-hydroxy-Tempo is particularly interesting. The partition between the two reactive sites leads to a rate constant of ca. 2×10^7 M^{-1} s^{-1} for insertion at the O–H bond. This is essentially the same rate constant as in the case of cyclohexanol. However, in this case the reaction is spin forbidden and must involve the access to the singlet surface at some point; while there has been considerable controversy[18,19,24] as to whether such access involves a preequilibrium or a surface crossing en route to products, it has generally been assumed that spin configuration plays a dominant role in the reaction, as expected from the Skell–Woodworth rules.[25] In principle, the insertion at the O–H site in 4-hydroxy-Tempo could be spin allowed (i.e., doublet + triplet → doublet) if sufficient interaction between the O–H and nitroxide centers takes place. However, the EPR parameters for 4-hydroxy-Tempo suggest that the interaction between the two sites is small.[20] While the magnitude of the relaxation of spin conservation rules seems unclear, our kinetic results show virtually no effect. For example, compare the $k_{insertion}$ values for cyclohexanol and 4-hydroxy-Tempo (Table I). We suggest that this reflects the fact that the dominant factor controlling differences in reactivity between singlet and triplet carbenes is their orbital occupancy, rather than the overall multiplicity.[26]

The absence of significant reactivity at the NH_2 center in 4-amino–Tempo is in full agreement with recent studies by Griller and Nazran[27] who observed low apparent triplet reactivities toward amines, with typical rate constants below 10^6 M^{-1} s^{-1}.

The essentially quantitative yields of benzophenone and 2,2,6,6-tetramethylpiperidine in the case of Tempo are indicative of very clean chemical processes. Thus, while benzophenone may be reexcited during the continuous photolysis experiments, the concentration of Tempo is probably sufficiently high to force its deactivation via

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[26] A few measurements were carried out in attempts to detect the carbonyl triplet state of 4-oxo-Tempo using laser photolysis. This could be successful if the ketone and nitroxide sites do not interact significantly. The experiment was unsuccessful. The fluorescence intensity from 4-oxo-Tempo is only about 4% of that of cyclohexanone, presumably indicating efficient intramolecular quenching of the singlet. This seems to suggest significant site "communication" at least in the case of the carbonyl singlet.

[27] Griller, D.; Nazran, A. S., unpublished.

quenching; as a result, no diphenylmethanol was detected in any of the samples. As for the amino radical, it is well-known not to undergo self-reaction, and while slow its dominant decay path seems to be H abstraction.[23]

Experimental Section

Materials. Diphenyldiazomethane (DPDM) was prepared from benzophenone by a standard procedure[28] and purified by sublimation under high vacuum. Isooctane (Aldrich, Gold Label) was used as received, while acetonitrile (Fisher, spectro grade) was distilled over calcium hydride. Acetonitrile-d_3 (Merck, Sharp and Dohme) was used as received. All the nitroxides were obtained from Aldrich and were purified by sublimation, with the exception of 4-amino-Tempo which was used as received.

General Methods. All quantitative GC analysis were carried out by using flame-ionization detectors and either packed (OV-101) or capillary columns (10 m, 0.2 mm id, equiv OV-101). The fact that nitroxides can be chromatographed readily was very useful. Diphenylmethane was used as an internal standard after verifying that it was not one of the products of reaction. GC/MS analysis were carried out by using a Hewlett-Packard Model 5995 instrument.

Preparative irradiations were carried out in a reactor equipped with 12 RPR-3000 lamps. The temperature in this reactor was typically 36 °C. The concentrations used in these experiments were the same used in the laser flash studies, with the nitroxide concentrations selected so that more than 90% of the carbene decayed via reaction with this substrate. This is regarded as very important in view of other carbene studies that suggest extensive product dependence with reagent concentration.[21] The irradiation times were as short as possible, while ensuring that DPDM had been totally consumed.

Product Studies. General Procedure. All solutions were purged by bubbling dry nitrogen and then irradiated for 7 min with 12 RPR-3000 lamps. After photolysis, 2 mL of solution was separated; the remainder was concentrated by distillation with a 15-cm vacuum-jacketed Vigreaux column. When ~5 mL remained, the residue was concentrated to <1 mL on a rotary evaporator. Quantitative GC analysis was carried out in the concentrated portions by using diphenyldiazomethane as internal standard. The yields of volatile products were determined from the aliquots separated before concentration. GC–MS analysis were also carried to confirm the identity of the products.

(1) Photolysis of DPDM and Tempo in Acetonitrile. (a) Solution: 50 mL; 1.2×10^{-3} M Tempo; 1.16×10^{-4} DPDM in acetonitrile. Three major products were detected: benzophenone and 2,2,6,6-tetramethylpiperdine in yields >95% based on DPDM. The third product corresponds to <1% conversion of Tempo and its MS shows M$^+$ at $m/z = 196$. (b) Solution: 20 mL; 1.6×10^{-3} M Tempo, 1×10^{-4} M DPDM is acetonitrile-d_3. The products were the same as **1a** (above). However, the MS of the third unidentified product showed M$^+$ at m/z 198 (to be compared with 196 in unlabeled acetonitrile). (c) Solution: 50 mL; 1.2×10^{-3} M Tempo in acetonitrile. One single product (<1% conversion) was detected; its retention time was the same as the unidentified product in experiments **1a** and **1b**. Its MS was identical with that of case **1a** with M$^+$ at 196 and ions (abundance) 41 (100), 69 (63), 55 (56), 56 (53), 42 (52), 156 (32), 58 (25), 109 (20).

(2) Photolysis of DPDM and Tempo in Isooctane. Solution: 75 mL; 1.5×10^{-2} M Tempo; 1×10^{-4} M DPDM in isooctane. Three major products were detected: 2,2,6,6-tetramethylpiperidine, benzophenone, and an unknown whose MS showed M$^+$ at m/z 269. The yield of benzophenone was >95% based on DPDM.

(3) Photolysis of DPDM and 4-Hydroxy-Tempo in Acetonitrile. (a) Solution: 50 mL; 1.5×10^{-3} M 4-hydroxy-Tempo; 1.2×10^{-4} DPDM in acetonitrile. Four major products were detected: 4-hydroxy-2,2,6,6-tetramethylpiperidine, benzophenone, the product of carbene insertion at the O–H site, and a fourth product whose MS showed M$^+$ at m/z 212. The yield of benzophenone was 87% based on DPDM and the ratio of oxygen abstraction to O–H insertion was ~16. (b) Solution: 50 mL, 1.5×10^{-3} M 4-hydroxy-Tempo in acetonitrile. Only one major product was detected with the same retention time and MS as the unidentified product in **3a**.

(4) Photolysis of DPDM and 4-Amino-Tempo in Acetonitrile. Solution: 50 mL; 1.9×10^{-3} M 4-amino-Tempo and 1.2×10^{-4} M DPDM in acetonitrile. Three major products were detected: 4-amino-2,2,6,6-tetramethylpiperidine, benzophenone, and an unknown whose MS showed intense ions at m/z 212 and 211. The yield of benzophenone was 90% based on DPDM. None of the higher molecular weight products (in total accounting for <2%) showed MS expected for the N–H insertion product.

(5) Photolysis of DPDM and Cyclohexanol in Acetontrile. Solution: 50 mL, 0.03 M cyclohexanol, 1.2×10^{-4} M DPDM. Only the O–H insertion product (IV) was observed in >95% yield.

Laser Photolysis. Laser flash experiments were carried out by using a Lumonics TE860-2 excimer laser operated with Xe–HCl mixtures for excitation. Due to the very dilute samples of DPDM used, it was necessary to flow the samples through the reaction cell made of 7 × 7 mm^2 Suprasil tubing. Typical flow rates were ca. 0.3 mL/pulse. The transient signals, initially captured by a Tektronix R-7912 transient digitizer were then transferred to a PDP-11/23 computer that controlled the experiment and provided suitable processing, storage, and hardcopy facilities. Further details on our laser facility have been provided elsewhere.[29]

Acknowledgment. Thanks are due to S. E. Sugamori for technical assistance, to D. Lindsay for carring out the GC/MS measurements, and to Professor N. J. Turro for providing a preprint of ref 7.

Registry No. Tempo, 2564-83-2; 4-hydroxy-Tempo, 2226-96-2; 4-amino-Tempo, 14691-88-4; diphenylcarbene, 3129-17-7; cyclohexanol, 108-93-0.

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