(Co)oxidation/cyclization processes upon irradiation of triphenylamine

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ABSTRACT

Irradiation of triphenylamine (Ph_3N) in nitrogen-flushed solution leads to 9-phenylcarbazole and two tetrahydroderivatives (1,2,3,4- and 1,2,7,8-) via disproportionation of the corresponding 4a,4b-dihydrocarbazole. In oxygen-equilibrated solution oxidative cyclization occurs through the intermediacy of a triplet peroxy diradical, which either abstracts a hydrogen atom intramolecularly or (mainly) cleaves back to the reagents. The role of the key intermediates is supported by DFT calculations and by trapping by triarylphosphines (that are thus efficiently oxidized, while preventing the cyclization of Ph_3N). The hydroperoxide, on the other hand, causes inefficient co-oxidation of sulfides.

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The electrocyclic rearrangement of stilbene and related aryl-alkenes is of great interest both as a synthetic approach to polycyclic derivatives and for the mechanistic issues involved.[1] This is probably the most in-depth studied reaction where photochemical and thermal processes follow opposite stereochemical courses,[1a] leading to either *trans* or *cis* relationship of the substituents at the ring fusion positions. When these are hydrogen atoms, oxidation may follow and leads to an aromatic derivative.[1c] Heteroatom-containing analogs of stilbene and other 6π electrons systems have been likewise studied intensively and are of equal interest on the same grounds. An example is the photocyclization of di-[2–4] and tri-phenylamines[3–5] that leads to dihydrocarbazoles, some of which are present among natural products,[6] or, by oxidation, to carbazoles, a class of heterocycles often employed in drugs,[7] dyes,[8] photoactive polymers,[9] and, OLEDs.[10] In particular, the photocyclization of triphenylamine (see Scheme 1) to 9-phenylcarbazole (**NPC**) has been reported[2e,3] in different organic solvents. From the mechanistic point of view, electrocyclic photocyclization is one of the few cases where the adiabatic course of a photoreaction (from the excited state of the reagent to the excited state of the product) has been documented. Thus, both time resolved spectroscopy analyses[5,11] and a computational investigation by the AM1-SCI method supported that cyclization from $^3Ph_3N$ (singlet–triplet intersystem crossing is almost quantitative in this

compound)[2e,3] led to trans-*N*-phenyl-4a,4b-dihydrocarbazole in the triplet state (represented by the diradical formula ^{3}**DHC**,[11] *path a*, Scheme 1) and this in turn crossed (*path b*) over to the singlet ground state, more stable by 3.9 kcal mol^{-1} (represented as **DHC$_0$**).[12] The last intermediate had a zwitterionic rather than diradical character and it was remarked that this was consistent with the fact that no spin trapping occurred in the presence of 5,5-dimethyl-1-pyrroline-*N*-oxide and *N-tert*-butyl-α-phenylnitrone.[11,13] It was formed efficiently, but mainly reverted back to Ph_3N (*path d*, >90%) and only in part underwent disproportionation (*path c*) to carbazole (**NPC**) and a tetrahydrocarbazole (**H$_4$-NPC**, of structure not known, notice that analogous *N*-methyldiphenylamine[2a] gives the 1,2,7,8-derivative).

In the presence of oxygen, aromatization of **DHC$_0$** to **NPC** occurred. It was found that the quantum yield of the oxidative cyclization (Φ_{cy}) increased from 0.04 to 0.09 (depending on the nature of the solvent) when changing from oxygen-free conditions to ca. 0.2 in air equilibrated solution.[3] Potentially, oxygen may interact with all of the sequentially formed intermediates, $^3Ph_3N$, ^{3}**DHC**, and **DHC$_0$**, and the overall yield appeared to result from the balance between quenching of $^3Ph_3N$ by molecular oxygen (producing $^1O_2$, with $\Phi = 0.63$ in benzene)[14] and the intervention of O_2 mediated paths making more efficient the formation of **NPC**. Hydrogen peroxide was also formed.[3] Understanding the role of oxygen in the aromatization step deserved, we thought, further attention, also because it seemed possible that some intermediates generated may oxidize other compounds under mild conditions. In view of the above, we decided to further pursue this issue and report

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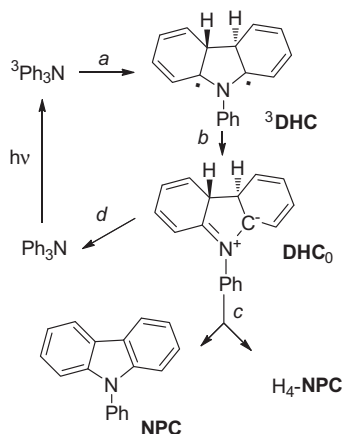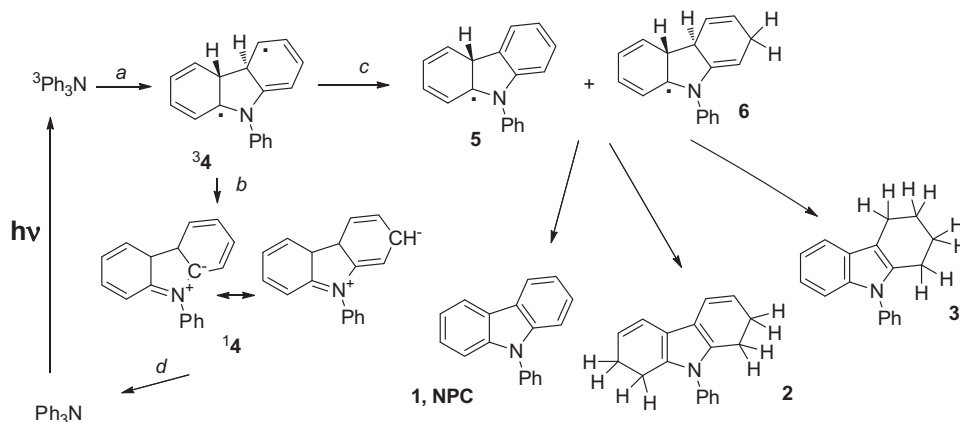
Scheme 1. Photochemical cyclization of triphenylamine (Ph₃N).

below a combined experimental and computational investigation about the photocyclization of triphenylamine in different solvents and in the presence of oxidation-liable substrates.

In our hands, irradiation of a nitrogen-flushed 1×10^{-2} M acetonitrile solution of Ph₃N led to N-phenylcarbazole (**1**) as the main product (53%) along with two tetrahydro-derivatives that were spectroscopically identified (see Scheme 2) as N-phenyl-1,2,7,8-tetrahydro- (**2**, 14%) and N-phenyl-1,2,3,4-tetrahydrocarbazole (**3**, 5%), containing respectively a doubly conjugated pyrrole and an indole aromatic system. Compounds **1**–**3** obviously arose from a dihydrocarbazole intermediate (**4**) the role of which was assessed by means of a DFT computational study at the (U)B3LYP level of theory, by using the integral equation formalism model (IEFPCM) for the solvent (acetonitrile). The Pople's basis set 6-311++G(2d,p) was adopted for all atoms (see ESI† for further details). This essentially confirmed the AM1-SCI results, though with some differences in the electronic distribution. Thus, singlet ^{1}**4** had a purely zwitterionic character (a mixture of two predominant mesoionic structures, as indicated in Scheme 2) and lay a mere 3.4 kcal mol^{-1} below the triplet ^{3}**4** (of diradical character, satisfactory represented by the single formula in Scheme 2). As mentioned, rearrangement to ^{3}**4** and ISC to ^{1}**4** mainly led to retro-cyclization to triphenylamine (*path d*). No intramolecular concerted path leading to an aromatic system was available and reasonably intermolecular hydrogen transfer took place leading to radicals **5** and **6** and to the observed products **1**–**3** from them.

The corresponding experiment with an oxygen-equilibrated solution gave **1** as the only isolated product, along with a small amount of highly polar products. In order to understand the mechanism of the oxidative photocyclization, the photoreaction of Ph₃N in the presence of potential oxygen acceptor was investigated. Sulfides and phosphines were chosen as suitable probes (see Scheme 3). The results are reported in Tables 1 and 2 and can be summarized as follows. Sulfides were co-oxidized to sulfoxides at a rate dependent on structure and conditions. The rate of the tri-phenylamine oxidative cyclization increased to a various extent (10–250%) and the rate ratio of sulfoxide versus carbazole formation was ⩾1 (from ca. 1.1 to 2.5). In contrast, irradiation of triphenylamine in the presence of either triphenylphosphine or tris-(2-methylphenyl)phosphine led to the corresponding phosphine oxides, but at the same time the formation of N-phenylcarbazole (**1**) was completely inhibited. A precise comparison between the oxidation rate of sulfides and phosphines was not feasible, since different irradiation conditions had to be adopted to avoid auto-oxidation of phosphines, but it was clear that the photooxidation of the latter substrates was at least five times faster than either oxidation of sulfides or oxidative photooxidation of TPA alone. These results pointed to the involvement of different intermediates in the reaction of the two traps.

Energy transfer to give singlet oxygen is energetically viable only by quenching of ^{3}Ph₃N (see above)[14] and not from ^{3}**4**, due to the low energy gap of the latter from ground state ^{1}**4**, much below that required for ^{1}O₂ formation (ca. 22 kcal mol^{-1}).[15a] If these were the only effect by oxygen, it would lead to quenching of the cyclization and oxygenation of the additives.[15b,c] The following evidences suggested that this was not a singlet oxygen reaction, however: (1) thus, under bona fide ^{1}O₂ conditions, ring-substituted triphenylphosphines are known to give phosphinates along with phosphine oxides,[16] contrary to what observed in the present case (see Table 1); (2) as for sulfides, sulfones are known to always accompany the sulfoxides, at least in polar aprotic and non-polar solvents, and benzyl sulfides do undergo both sulfoxidation and oxidative cleavage to benzaldehyde in protic media, again differently from what observed under the present conditions (see Table 2).[17] An alternative mechanism is that the diradical character of dihydrocarbazole ^{3}**4** makes viable a chemical quenching of the intermediate by molecular oxygen (*path e* in Scheme 3). Actually, the interaction of ^{3}**4** with ground state (triplet) oxygen can result in a singlet, a triplet, or a quintet. Computing the energy of all of the possible combinations demonstrated that the most favored path led to a chemically bonded adduct with triplet multiplicity that was formed through an almost thermoneutral process ($\Delta G° = 0.24$ kcal mol^{-1}, through a transition state that was located at 6.7 kcal mol^{-1}, see Scheme 4). More precisely, taking into account both the regiochemistry and the stereochemistry of such

Scheme 2. Cyclization of Ph₃N under O₂-free conditions.
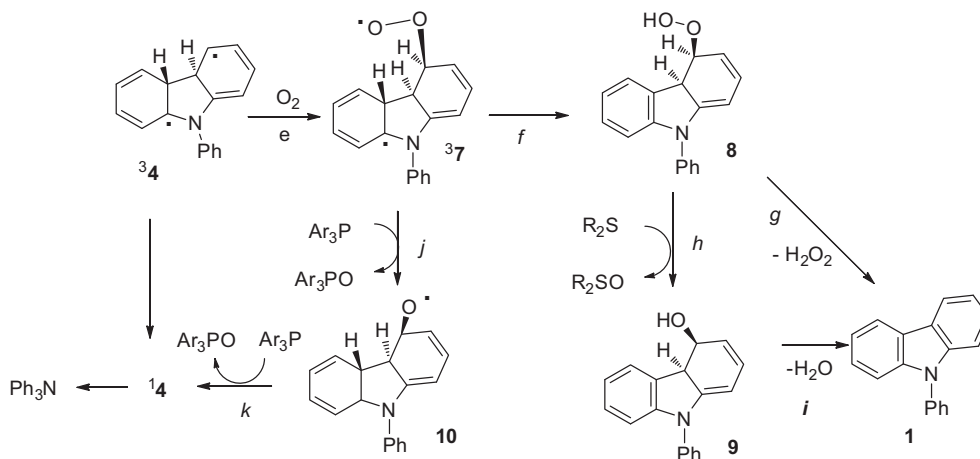
Scheme 3. Proposed mechanism for the co-oxidation of triphenylphosphine and sulfides during the photocyclization of triphenylamine.

Table 1
Rates of co-oxidation of aryl sulfides (µmol min^{-1}) upon irradiation in the presence of Ph$_3$N; in parentheses, the amount of N-phenylcarbazole (1) formed (µmol min^{-1})[a]

	MeCN	MeCN/H$_2$O 9/1	TFE	CH$_2$Cl$_2$
Neat solvent	(.049)	(.16)	(.43)	(.104)
PhSMe → PhSOMe	0.029(.075)	.17 (.21)	0.53 (0.19)	.087 (.11)
4-MeOC$_6$H$_4$SMe → 4-MeOC$_6$H$_4$SOMe	.075 (.11)	.31 (.24)	.24 (.074)	.17 (.13)
PhCH$_2$SEt → PhCH$_2$SOEt	.21 (.096)[b]	.48 (.20)	.22 (.075)	.45 (.10)
Ph$_2$S → Ph$_2$SO	.023 (.13)	<.01 (.19)	.013 (.042)	.031 (.098)

[a] 5×10^{-3} M solution of Ph$_3$N irradiated in the presence of the chosen sulfide (10^{-2} M) at 366 nm (4×15 W phosphor-coated lamps).
[b] PhCHO (.091 µmol min^{-1}) was also observed.

Table 2
Rates of co-oxidation of aryl phosphines (µmol min^{-1}) upon irradiation in the presence of Ph$_3$N; in parentheses, the amount of N-phenylcarbazole 1 formed (µmol min^{-1})[a]

	MeCN	MeCN/H$_2$O 9/1	TFE	CH$_2$Cl$_2$
Ph$_3$P → Ph$_3$PO	0.121 (−)	0.188 (−)	0.033 (−)	0.091 (−)
(o-Tol)$_3$P → (o-tol)$_3$PO	0.042 (−)	0.052 (−)	0.049 (−)	0.054 (−)

[a] 5×10^{-3} M solution of Ph$_3$N irradiated in the presence of the chosen phosphine (10^{-2} M) at 366 nm (focalized, filtered light; under these conditions no oxidation of the phosphine took place in the absence of triphenylamine).
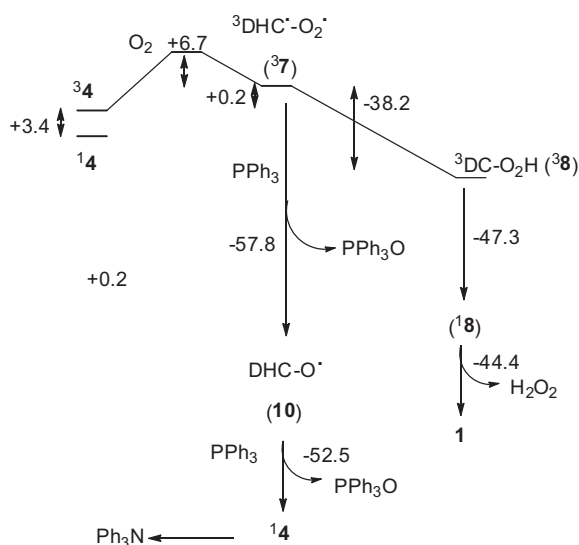
Scheme 4. Energy change in the observed reactions (values in kcal mol^{-1}).

adducts, six isomeric structures can be envisaged for this reaction (see Figs. S1–S6 in the Supplementary information). The most stable isomer resulted from attack at position 3 (diradical ^{3}7 in Schemes 3 and 4). In turn, the generated intermediate could undergo intramolecular hydrogen abstraction and give a hydroperoxide (8, path f in Scheme 3) through a largely exergonic (−38.2 kcal mol^{-1}) process (see Scheme 4).

The obtained hydroperoxide underwent aromatization by hydrogen peroxide elimination (path g), a process presumably encountering a significant barrier and occurring at room temperature a rather slow radical chain mechanism.[18] In the presence of sulfides, however, oxygen transfer to form sulfoxides occurred and the resulting hydroxy derivative 9 (path h) underwent dehydration to give carbazole 1. Thus, with sulfide dihydrocarbazole aromatization and donor oxidation were coupled and the result depended on the nature of the substrate (e.g., diphenylsulfide was much less efficient than a mixed aromatic–aliphatic sulfide or a dialkyl sulfide such as PhCH$_2$SCH$_2$CH$_3$, see Table 1). On the other hand, the precursor of hydroperoxide 8, viz. diradical 7, was another potential oxygen-donating species. It appears reasonable that the more nucleophilic phosphines were able to trap such radicals in efficient competition with intramolecular H-abstraction (path j vs path f). Indeed, the reactivity of peroxy radicals with phosphines has been previously demonstrated.[19a] As an example, oxidation of triphenylphosphine by t-butylperoxide occurs at a rate of 10^2 M^{-1} s^{-1} at room temperature more than two orders of magnitude larger than that with sulfides (0.73 M^{-1} s^{-1})[19b] and likewise catalyzed oxidation by hydrogen peroxide is markedly faster.[20] Also in this case, DFT calculations were carried out and demonstrated that in the presence of phosphines oxygen transfer both from diradical 7 and from the resulting radical 10 is strongly exergonic (path j and k, $\Delta G° = -71.3$ and -45.5 kcal mol^{-1} respectively, the P—O bond formation being the driving force of the

process). Thus, two oxygen atoms were sequentially transferred to the phosphine and led back to [1]4 that, as previously indicated, underwent retrocyclization to Ph_3N. This mechanism is closely analogous to that determined for the oxidation of triarylphosphines by α-aminoalkylperoxy radicals[19a] and in accord with the experimental evidence indicating that the oxidation of phosphines inhibits the conversion of [3]7 to the carbazole. With a much more efficient process, *path j* competes with both *path f* and with unproductive decay to [1]4.

In conclusion, triplet dihydrocarbazole ([3]4) adds O_2 to form two potentially oxidizing species. The first formed peroxy diradical (7) has a strong electrophilic character, but a short lifetime due to the decay to [1]4, and is trapped by nucleophilic phosphines to which both atoms of oxygen are transferred. Notice that the structure of peroxy diradical 7 corresponds to the chemical (rather than physical) activation of oxygen as originally formulated by Schenck for photosensitized oxidations (Sens + hν → ·Sens· + O_2 → ·Sens-O–O·).[21] Sulfides are poor traps and in that case rearrangement of short-lived 7 to hydroperoxide 8 occurs faster than oxygen transfer. Sulfides do trap a persistent intermediate such as 8 and subsequent dehydration leads to aromatized 1. Thus oxidative cyclization and sulfide co-oxidation are coupled. The results obtained may have a potential significance from both the synthetic and mechanistic point of view. In fact, the Ph_3N oxidative cyclization follows a complex path and involves various active intermediates that may find application in organic synthesis, for example for the selective oxidation of poly-functionalized compounds.

Acknowledgements

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.03.086.

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