

Comparison of Phenylcarbene and Phenylnitrene¹

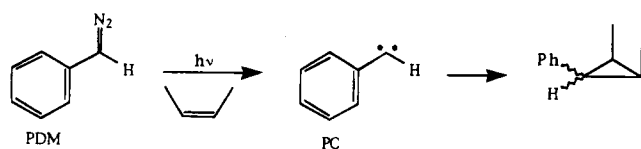
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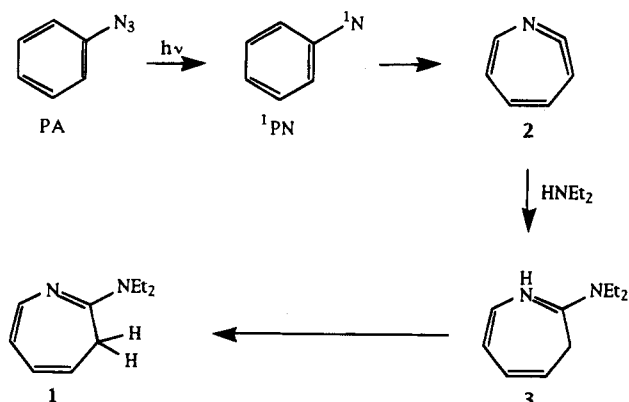
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I. Introduction

Over 20 years ago a wise man wrote that "the organic chemist, for all his modern sophistication, remains fundamentally a maker of compounds."² This statement still rings true and continues to color the language that organic chemists use in casual conversation. Phenyl diazomethane (PDM) and phenylcarbene (PC) are called "good" reagents because they cleanly produce carbene adducts in high yield. PC is liberated upon photolysis of PDM and reacts efficiently with alcohols and alkanes and largely stereospecifically with alkenes.³ In contrast, the photolysis of



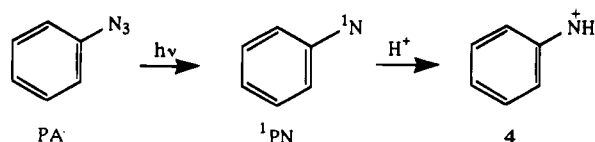
phenyl azide (PA) in alcohols, alkenes, and aromatic and alkane solvents at ambient temperature fails to give more than trivial yields of adducts of phenylnitrene (PN).⁴ A dark polymeric tar is formed instead. The tar can be oxidized to form an electrically conducting polymer, but this fails to endear phenylnitrene to the hearts of organic chemists.⁵ In contrast to phenylcarbene, phenylnitrene as a reagent is never described with complimentary adjectives. The only preparatively useful photochemical reaction of phenyl azide takes place in diethylamine to form azepine 1, in a reaction discovered by Doering and Odum.⁶



In fact there is only one report that we are aware of in which a reagent (the proton) efficiently traps

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singlet phenylnitrene (¹PN) in solution prior to its expansion to ketenimine 2 to form the phenylnitrenium ion (4).⁷



It is the purpose of this Account to answer a simple question: Why is PN such a disappointing reagent in preparative chemistry even though its closely related analog, PC, is used routinely? What makes PC "good" and PN "bad"? The answer has been revealed by chemical analysis of reaction mixtures, spectroscopy, and kinetic studies performed in several laboratories.

II. Kinetics and Spectroscopy of Phenylcarbene

Phenylcarbene has been studied by matrix EPR,⁸ UV-vis,⁹ fluorescence,¹⁰ and IR⁹ spectroscopy. There is unanimous agreement that the carbene has a triplet ground state, and that the two bonds of the carbene carbon are not collinear. The optical spectrum of ³PC greatly resembles that of benzyl radical, implying that ³PC is planar and has an extended π system. Phenylcarbene has not been observed by spectroscopists in the gas phase perhaps because UV photolysis of PDM releases a vibrationally hot carbene which suffers rearrangement and/or fragmentation prior to relaxation. This is a pity because high-resolution gas phase spectroscopy can, in principle, provide the precise

(1) This paper is dedicated to Professor Jerome A. Berson in celebration of his 70th birthday, in recognition of his contributions as scientist, educator, mentor, and role model.

(2) Berson J. A. *Accs. Chem. Res.* **1972**, *5*, 406.

(3) The chemistry of phenylcarbene has been reviewed. Baron, W. J.; DeCamp, M. R.; Hendrick, M. E.; Jones, M., Jr.; Levin, R. H.; Schn M. B. *Carbenes*; Jones, M., Jr., Moss, R. A., Eds.; Wiley: New York 1973; Vol. 1, pp 163-73.

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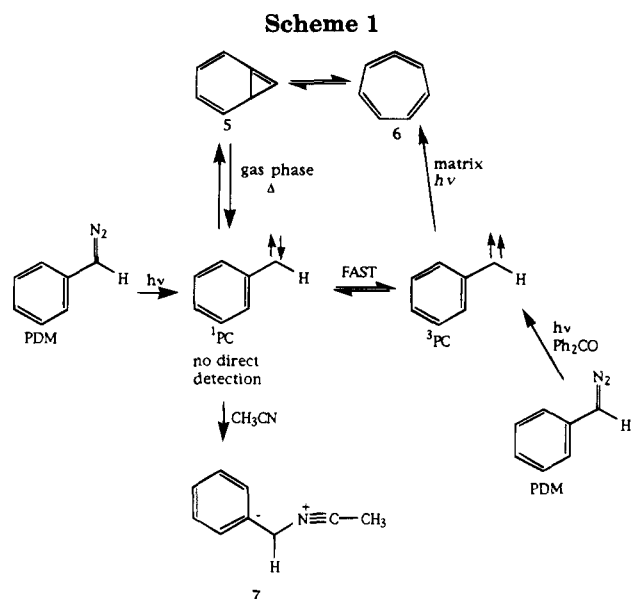
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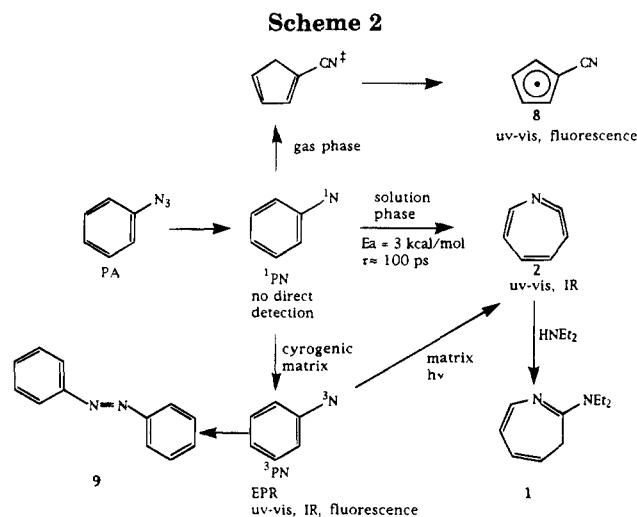


geometric structure of ^3PC . Singlet phenylcarbene has, to date, not been detected by any spectroscopic method.

The chemistry of PC is largely consistent with rapid interconversion of ^1PC and ^3PC .³ Direct and triplet-sensitized photolysis of PDM, analogs, and derivatives¹¹ generally produces the same mixture of products even in reactive solvents; thus the interconversion of their spin states is more rapid than chemical reaction of ^1PC or ^3PC with typical solvents. Intersystem crossing (ISC) rates of ^1PC and ^3PC are likely to be sub-nanosecond as per diphenylcarbene¹² and fluorenylidene.¹³

The UV spectrum of ^3PC falls underneath that of PDM, thereby complicating laser flash photolysis studies. However, ^1PC reacts with acetonitrile and pyridine to produce easily detected ylides (e.g., **7**, Scheme 1). The lifetime of the spin-equilibrated mixture of PC in acetonitrile or alkane solvents is certainly less than 20 ns and is probably more like 1–2 ns.¹⁴

Decomposition of PDM (or related precursors) in the gas phase at high temperature initiates the “phenylcarbene rearrangement”, which is mediated by highly strained intermediates **5** and **6** (Scheme 1).¹⁵ Tetraene **6** can be generated by low-temperature photolysis of ^3PC and can be isolated in inert matrices at cryogenic temperatures and characterized by infrared spectroscopy.⁹ Azirine **5** has not been detected directly. Very recent calculations suggest^{15e} that it is not a minimum



on the C_7H_6 surface and should not be shown as an intermediate in Scheme 1.

III. Kinetics and Spectroscopy of Phenylnitrene and Related Species

In 1980 the mechanistic/spectroscopic literature relating to the photochemistry of phenyl azide was truly bewildering and full of conflicting “facts”. The problem, in hindsight, is that there are several intermediates: ^3PN , ketenimine **2**, and cyanocyclopentadienyl radical (**8**), all of which absorb between 300 and 400 nm (Scheme 2). It is economical to write that photolysis of PA releases ^1PN , a species which has never been directly observed and whose fate depends upon the environment. In the gas phase it is formed vibrationally hot and ^1PN can explore the $\text{C}_6\text{H}_5\text{N}$ surface. It can likely undergo many reversible rearrangement processes. Eventually it will isomerize over a large (>30 kcal/mol) barrier¹⁶ in the gas phase to form cyanocyclopentadiene, the global minimum on the $\text{C}_6\text{H}_5\text{N}$ surface. This compound is also formed vibrationally hot and sheds a hydrogen atom to form a radical. This radical is the spectroscopically active species produced in the gas phase. The absorption and emission spectra of this radical were originally¹⁷ attributed to ^3PN , which influenced future analysis of transient spectra thought at the time to be due to ^3PN .¹⁸ Cullin and Miller *et al.* made the currently accepted spectroscopic assignment following isotopic labeling, independent generation of the radical, and vibrational–rotational analysis of its spectrum.¹⁹ The gas phase spectroscopic work is now in complete accord with the pioneering gas phase pyrolysis work of Wentrup and co-workers.¹⁶ Singlet phenylnitrene does not ring contract in solution to cyanocyclopentadiene because of the large barrier. In this regard the chemistry of ^1PN resembles that of ^1PC .

In the solution phase, ^1PN is immediately vibrationally deactivated and ring expands rapidly (~10–100 ps, ambient temperature) over a 3 kcal/mol barrier to form ketenimine **2**.²⁰ Upon photolysis of PA at very low temperature, the ring expansion of ^1PN is suppressed, and relaxation of ^1PN to ^3PN , a radiationless

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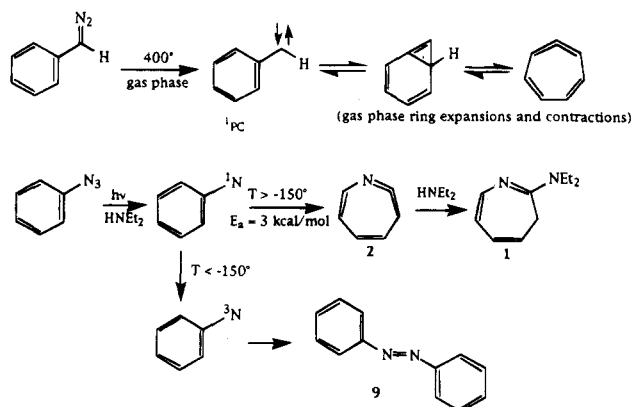
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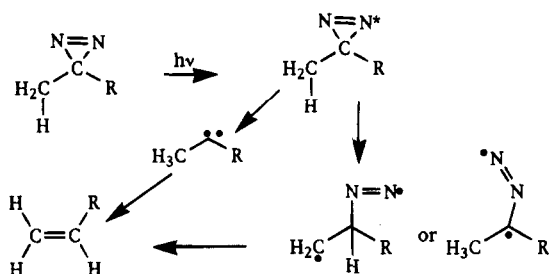
transition with a low probability factor but zero activation barrier to surmount, becomes dominant. Triplet phenylnitrene absorbs out to 500 nm and is very light sensitive.²⁰ It is easily photolyzed in matrices to form ketenimine **2**, the transient formed by flash photolysis of PA in solution.²⁰ This hampered efforts to get a clean matrix UV-vis absorption spectrum of triplet phenylnitrene. Ketenimine **2** has been characterized by matrix IR (1890 cm^{-1})²¹ and UV spectroscopy (320–360 nm, broad);²⁰ ³PN has been characterized by matrix EPR,²² IR,²³ and UV²⁰ spectroscopy (310, 340, 500 nm). In the solution phase, ketenimine **2** can react with itself or with phenyl azide to form polymeric tar.^{4,5,20}

Quite simply one of the basic differences between ¹PN and singlet phenylcarbene (¹PC) boils down to their relative ease of rearrangement. Thermal ring expansion of ¹PC is known only in the gas phase and requires hundreds of degrees centigrade.¹⁵ Ring expansion of ¹PN is faster than nearly every bimolecular process in solution even at -150°C . Below -150°C relaxation of ¹PN to ³PN becomes the dominant process.²⁰

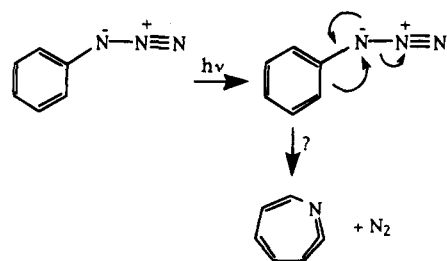


Thus photolysis of PA, in the presence of diethylamine, above -150°C , produces adduct **1**, but below this temperature, azobenzene (**9**), the product of triplet nitrene dimerization, is formed. (These product studies led to the deduction of the 3 kcal/mol barrier to ring expansion.)²⁰ However, this cannot be the whole story. If ¹PN was as reactive as ¹PC with alkenes ($k \approx 10^9 \text{ M}^{-1} \text{ s}^{-1}$), then in neat alkene ($\sim 10 \text{ M}$), singlet phenylnitrene should be a trappable species even if its lifetime is only 100 ps.

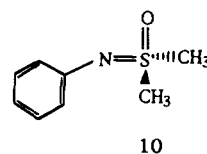
Our laboratory and other earlier research groups have argued that the photolysis of nitrogenous precursors of carbene (e.g., diazirines or diazo compounds) is complicated by rearrangement processes that mimic carbene processes.²⁴ One can try to explain the azide



photochemistry in a similar manner, and call the excited singlet state of phenyl azide the branching point, rather than singlet phenylnitrene.



If this mechanism is correct, then ¹PN is never formed upon photolysis of PA, and this explains why ¹PN cannot be trapped with alkenes. However, photolysis of **10**, an independent $\text{C}_6\text{H}_5\text{N}$ precursor, exhibits the same temperature dependent photochemistry as does PA.²⁵



Thus, while we cannot exclude the singlet excited state of PA (¹PA*) as the branching point, one must be willing to then postulate that ¹10* is also a branching point and, by coincidence, has the same temperature dependence as ¹PA*.

The basic question remains: Why is ring expansion of singlet phenylnitrene so much faster than that of singlet phenylcarbene?

There are at least two other critical questions as well. Singlet and triplet ¹PC interconvert very rapidly.^{3,11} ISC in both directions is more rapid than bimolecular carbene chemistry. Direct and triplet-sensitized photolysis of PDM in the presence of carbene traps gives the same mixture of products.^{3,11} Interconversion of ¹PN and ³PN is slow, if it happens at all in solution. Furthermore, triplet carbenes add to alkenes and dienes and readily abstract hydrogen atoms from donors.^{3,4} Triplet nitrenes do not. Singlet phenylcarbene inserts into CH bonds and adds to double bonds. Singlet phenylnitrene does not, possibly because ring expansion is so fast. Yet the absolute rate constants of singlet nitrene reactions with alkenes are probably smaller than those of singlet phenylcarbene (*vide infra*). Finally, what can an organic chemist do to make the bimolecular reactions of a singlet aryl nitrene more efficient?

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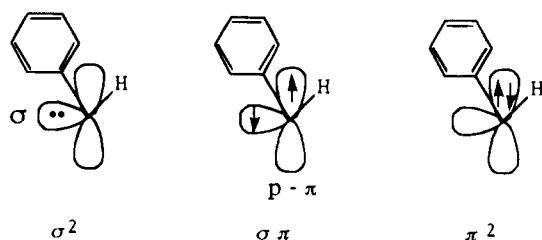
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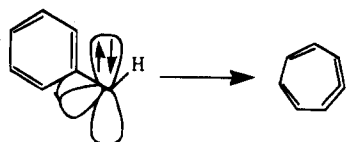
Simple answers to these basic questions have been advanced and will be the subject of the remainder of this Account.

IV. Simple and *ab Initio* Molecular Orbital Theory

The geometry of ^1PC has not been determined by experiment. Dannenberg's AM1 calculations find that the surface is rather flat; the geometry of ^1PC is quite floppy.²⁶ Recent *ab initio* calculations agree.^{15e} For the sake of simplicity, let's think of ^1PC as planar and with sp^2 hybridization and speak in terms of approximate descriptions of the electronic states.

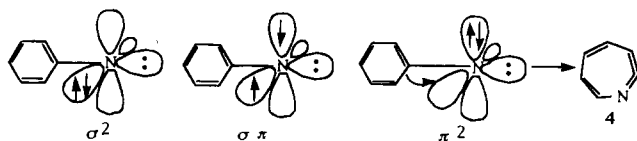


In this geometry and hybridization of ^1PC the two nonbonding molecular orbitals (NBMOs) must have very different energies. By analogy to singlet methylene²⁷ we expect that the σ^2 configuration is the lowest singlet configuration of PC followed by the open-shell $\sigma\pi$ configuration. Clearly the highest energy configuration will be π^2 . This configuration places both electrons in the highest lying orbital and maximizes electron-electron repulsion with no offsetting benefits. Perhaps it is the high-lying state with the approximately π^2 configuration that is responsible for concerted ring expansion. This reaction can proceed by sliding a pair of electrons into the empty adjacent, in-plane σ orbital.



Thus the reluctance of ^1PC to ring expand in solution may be the result of the need to access a very high energy configuration of the singlet carbene, or of serious distortion of ^1PC away from planarity.

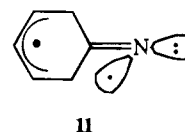
On the other hand, it is convenient to think of ^1PN as planar and approximately sp hybridized with the nitrogen lone pair in a $\sigma\pi$ orbital and two nearly degenerate π orbitals, σ and π .



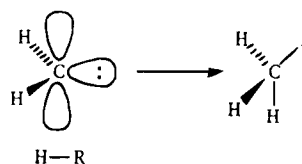
Because the two p orbitals are nearly degenerate, intuition and *ab initio* theory²⁸ predict that, unlike the

PC case (we presume), $\sigma\pi$ is the lowest singlet configuration of ^1PN . It also seems clear that the π^2 configuration, which seems prone to ring expansion, is not so high in energy relative to the σ^2 and $\sigma\pi$ configurations of ^1PN than is its ^1PC counterpart. This is because whereas the σ orbital of ^1PC is very much lower in energy than the p- π orbital of the carbene, the two nonbonding MOs of ^1PN are nearly degenerate. Thus rearrangements of ^1PN are faster than those of ^1PC .

Borden *et al.*^{28b} suggest that the most realistic resonance structure for ^1PN is iminyl biradical 11.



The concerted insertion reactions of singlet carbenes are often thought to involve the coordination of the empty p- π orbital of a singlet carbene with a pair of electrons in a σ or π bond.²⁹ Clearly this type of



concerted reaction is not possible for the open-shell singlet nitrene and explains the failure of ^1PN to add to alkenes or to insert into CH bonds. The rate constants for these reactions of singlet nitrenes must be much smaller than those of singlet carbenes.

Intersystem Crossing Rates. All evidence suggests that ^1PC to ^3PC ISC occurs rapidly with $k_{\text{ISC}} \geq 10^9 \text{ s}^{-1}$.^{3,11-13} Spin orbit coupling (SOC) is the likely mechanism of ISC and is maximal in the lower energy σ^2 configuration of ^1PC . ISC in this configuration is allowed because two orthogonal zwitterionic orbitals are coupled, according to the model of Salem and Rowland.³⁰ However, ISC mediated by the spin-orbit interaction is forbidden in the open-shell, lowest energy $\sigma\pi$ configuration of ^1PN , which results in a low intersystem crossing rate ($\sim 10^{6-7} \text{ s}^{-1}$). Furthermore, the fact that the two singly occupied MOs of ^1PN occupy very different regions of space also contributes to the slow rate of ISC.

Singlet-Triplet Energy Gaps. Finally, the difference in ISC rates also reflects the substantial difference in the singlet-triplet separation of PC and PN. Kinetic studies and chemical trapping studies of PC suggest that ΔH_{ST} is small, probably less than 2 kcal/mol at ambient temperature.^{3,10,11} However, spectroscopy^{28c} and theory^{28a,b} agree that ΔH_{ST} of PN is large, approximately 17–18 kcal/mol. As the rate of a radiationless transition (e.g., ISC) will be fastest when the energy separation between the states to be mixed is smallest, theory predicts slower ISC rates of ^1PN relative to ^3PN .³⁰

These differences in ΔH_{ST} can also be explained by simple theory. ^1PC receives some stabilization, relative to ^3PC , because both electrons and not just one reside in the lower energy σ orbital. This differential stabilization does not exist in ^1PN and ^3PN as both

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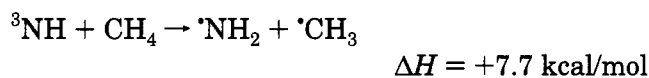
states have the same orbital occupancy ($\sigma\pi$). Thus ΔH_{ST} in PN is large because the reduction in electron–electron repulsion in ^3PN relative to ^1PN is not offset by placing two electrons in a very low energy orbital, as is the case in PC. This effect is amplified by the increased electron–nuclear attraction in nitrogen relative to carbon which draws the nonbonding electrons closer to the nucleus and increases electron–electron repulsion.

Triplet Phenyl Nitrene Is Rather Unreactive. As mentioned previously, triplet phenylnitrene does not add to alkenes or dienes and abstracts hydrogen atoms from alkanes rather slowly relative to triplet arylcarbenes. This effect probably has a thermodynamic origin.

The reaction of triplet methylene with methane is exothermic,³¹



but the corresponding reaction of triplet nitrene with methane is actually endothermic,



because the second bond dissociation energy of ammonia is rather small.³² We see no reason why this analysis should not extrapolate to ^3PN and ^3PC and explain the low reactivity of ^3PN .

Singlet carbenes are typically 3–4 orders of magnitude more reactive than triplet carbenes. Because the singlet–triplet gaps of arylcarbenes are small and ISC rates are large, the triplet carbene can often serve as a reservoir for an easily accessible, highly reactive singlet carbene. The lifetimes of certain ground state triplet arylcarbenes, such as fluorenylidene, can be as short as 1 ns in solution and controlled entirely by reactions of the low-lying singlet state.¹³ This is not true for arylnitrenes. Triplet arylnitrenes will not reform more reactive singlet states because the singlet–triplet gap (ΔH_{ST}) is much too large (17 kcal/mol).²⁸

V. Fluorine Effect

Over 20 years ago Banks and co-workers discovered that pyrolysis of polyfluorinated aryl azides in alkane, alkene, or aromatic solvents produces nitrene adducts in reasonable yields.³³ Recall that this is not possible with phenyl azide.⁴ The work of Banks's group (which included some photochemical studies) stimulated our laboratory³⁴ and that of Keana³⁵ to study the photochemistry of polyfluorinated aryl azides in detail.

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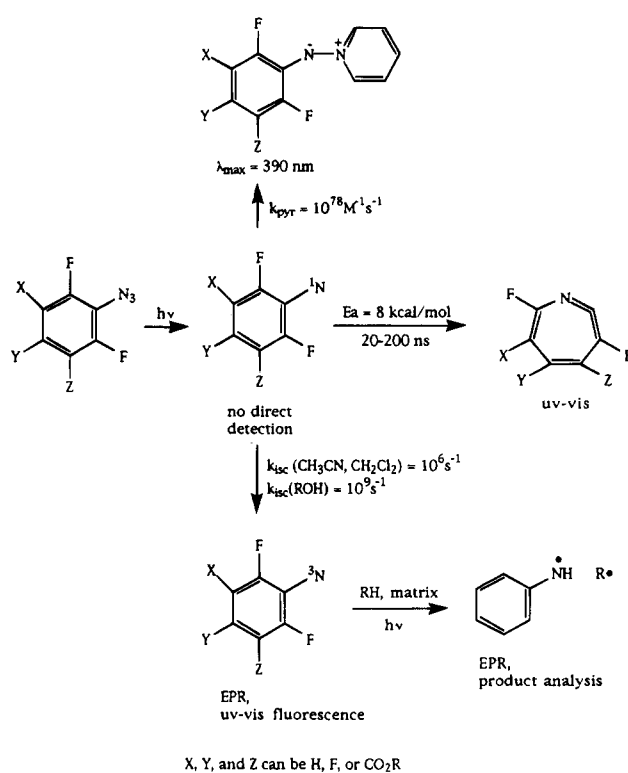
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(34) (a) Poe, R.; Grayzar, J.; Young, M. J. T.; Leyva, E.; Schnapp, K. A.; Platz, M. S. *J. Am. Chem. Soc.* **1991**, *113*, 3209. (b) Poe, R.; Schnapp, K. A.; Young, M. J. T.; Grayzar, J.; Platz, M. S. *J. Am. Chem. Soc.* **1992**, *114*, 5054. (c) Young, M. J. T.; Platz, M. S. *J. Org. Chem.* **1991**, *56*, 6403. (d) Schnapp, K. A.; Poe, R.; Leyva, E.; Soundararajan, N.; Platz, M. S. *Bioconjugate Chem.* **1993**, *4*, 172. (e) Schnapp, K. A.; Platz, M. S. *Bioconjugate Chem.* **1993**, *4*, 178. (f) Soundararajan, N.; Platz, M. S. *J. Org. Chem.* **1990**, *55*, 3640.

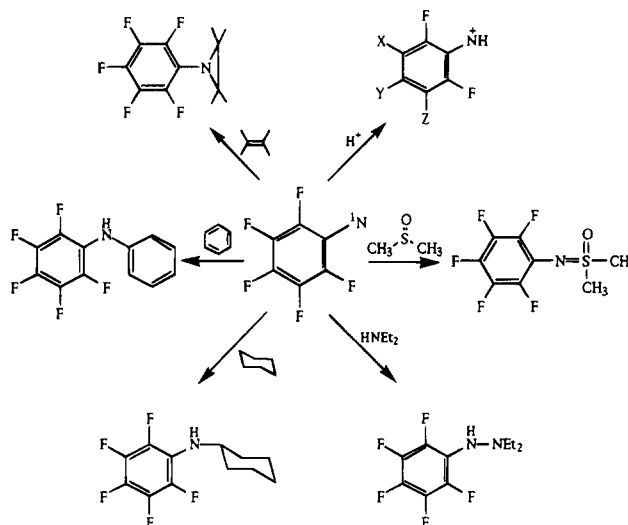
(35) (a) Keana, J. F. W.; Cai, S. X. *J. Fluorine Chem.* **1989**, *43*, 151. (b) Keana, J. F. W.; Cai, S. X. *J. Org. Chem.* **1990**, *55*, 2034. (c) Cai, S. X.; Keana, J. F. W. *Bioconjugate Chem.* **1991**, *2*, 28. (d) Cai, S. X.; Glenn, D. R.; Keana, J. F. W. *J. Org. Chem.* **1992**, *57*, 1299.

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Scheme 3



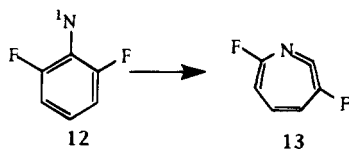
Scheme 4



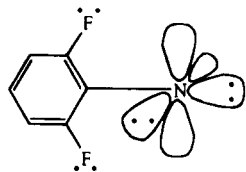
Our work can be summarized in Schemes 3 and 4. Singlet (pentafluorophenyl)nitrene can be captured by a wide range of reagents. The pyridine ylide is stable, and it can be isolated and characterized by X-ray crystallography in fact. It is intensely absorbent ($\lambda_{\text{max}} = 390 \text{ nm}$) and can be used to probe the dynamics of the singlet nitrene.³⁴ Placement of fluorine atoms at positions 2 and 6 of the aromatic ring, relative to the position of the nitrene nitrogen, raises the barrier to ring expansion to 8 kcal/mol and extends the singlet nitrene lifetime into the range of tens or hundreds of nanoseconds at ambient temperature.³⁶ The greater lifetime of the singlet nitrene allows time for efficient bimolecular chemistry.

The increased barrier to ring expansion may of course have its origin in electron configuration effects or in thermodynamics.

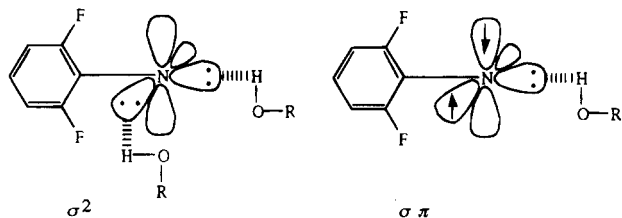
Fluorine may destabilize the ketenimine perhaps and make ΔH and ΔH^\ddagger for ring expansion larger than



in ^1PN . Alternatively the π -donating ability of fluorine may dramatically stabilize the σ^2 configuration relative to the reactive π^2 and the lowest energy $\sigma\pi$ configurations. Thus fluorine substituents may make the arylnitrene look more like phenylcarbene, where ring expansion is unknown in solution. High-level *ab initio* calculations of **12** and **13** (and their 3,5-disubstituted isomers) where there is no fluorine effect would be most welcome and instructive!



Much to our surprise we found that ISC of fluorinated arylnitrenes is catalyzed by alcohols.³⁴ Ethers and polar nitrile solvents are ineffective at stimulating this process. We postulate that alcohols stabilize the σ^2 configuration of the nitrene relative to the $\sigma\pi$ configuration by hydrogen bonding.³⁶



As the closed-shell σ^2 configuration becomes more accessible by stabilization through hydrogen bonding, spin-orbit-mediated ISC becomes allowed and rapid

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just as in ^1PC . Hydrogen bonding makes the nitrene singlet look more like a carbene.

We have studied the chemistry, kinetics, and spectroscopy of (pentafluorophenyl)carbene.³⁷ In contrast to the phenylnitrene scenario, polyfluorination has little to no effect on the kinetics and chemistry of the carbene. This is in accord with our simple analysis. Singlet (pentafluorophenyl)carbene and phenylcarbene already "look" like carbenes.

Following the lead of McClelland⁷ and Wirz³⁸ we have studied the protonation of singlet fluorinated arylnitrenes.³⁹ The reaction is facile and general and produces nitrenium ions with extremely long lifetimes. The polyfluorinated arylnitrenium ions have singlet ground states³⁹ as does parent phenylnitrenium ion.⁴⁰ Again fluorinated singlet arylnitrenes look like singlet carbenes which can also be protonated by acids to form carbocations.⁴¹

VI. Concluding Remarks

Much of the interpretation presented herein is based on very simplistic models and as such is highly speculative. High-level *ab initio* molecular orbital calculations of PC and of fluorinated arylnitrenes and ketenimines are urgently needed to confirm or discredit these ideas. It is time for the new generation of fast spectroscopists to find singlet phenylnitrene and singlet phenylcarbene and for high-resolution gas phase spectroscopists to find the triplet states.

Although we are confident of the general mechanistic outline, experimental studies of azide photochemistry are still incomplete. Direct measurement of ring expansion rates of nonfluorinated arylnitrenes by picosecond spectroscopy has barely begun. Kinetic studies need to be coupled with photoacoustic spectroscopy to determine ΔH for ring expansion. These results will generate a deeper understanding of nitrene structure and reactivity.

However, this area is no longer a bewildering compilation of seemingly conflicting observations, and one can truly begin to design azides for particular applications. This is particularly true in the area of photoaffinity labeling. Several reports of new polyfluorinated aryl azide reagents have appeared,^{34,35,42} and I, for one, look forward to learning how these reagents can be used to reveal the structure and function of biological molecules.

It is a pleasure to acknowledge the hard work of my students whose names appear in the various references, the stimulating contributions of my collaborators, Professors Jakob Wirz (Basel, Switzerland) and Terry Miller (Ohio State), and valuable discussions with Professors Schuster, Sheridan, and Gaspar. Support of this work by the National Institutes of Health (nitrenes, GM-34823) and the National Science Foundation (carbenes, CHE-8814950) is gratefully acknowledged.

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