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Structure of Dimesitylcarbene[1]

A. S. Nazran, E. J. Gabe, Y. LePage, D. J. Northcott,
J. M. Park, and D. Griller*

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

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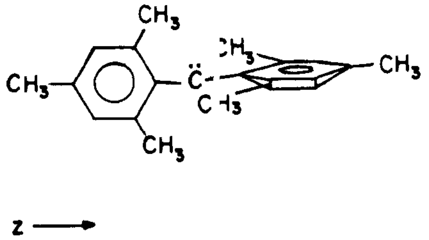
In 1964 Zimmerman and Paskovich[2] described attempts to modify the chemical reactivity of diarylcarbenes by designing structures that were sterically congested.[3] They found unusual chemical properties for dimesitylcarbene (I).



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In solution, at low temperatures, this carbene did not react with the parent diazo compound to give azine but dimerized (reactions 1 and 2, Mes = 2,4,6-trimethylphenyl).[2,4] It was also relatively

$$\mathrm{I} + (\mathrm{Mes})_2\mathrm{C}{=}^{+}\mathrm{N}{=}\mathrm{N}^{-} \rightarrow (\mathrm{Mes})_2\mathrm{C}{=}\mathrm{N}{-}\mathrm{N}{=}\mathrm{C}(\mathrm{Mes})_2 \qquad (1)$$

$$2\mathrm{I} \rightarrow (\mathrm{Mes})_2\mathrm{C}{=}\mathrm{C}(\mathrm{Mes})_2 \qquad (2)$$

unreactive toward secondary carbon-hydrogen bonds in solvent molecules and at high temperatures decayed by attack at an ortho-methyl group;[2,4] a reaction that is not observed for (2-methylphenyl)phenylcarbene.[5] The chemistry found for dimesitylcarbene is therefore in sharp contrast with that found for other diaryl carbenes.[6,7]

In this work, we have used electron paramagnetic resonance (EPR) spectroscopy to study the structure of dimesitylcarbene and have found results that complement its unusual chemistry.

Dimesityldiazomethane[2] was used as a precursor for I. X-ray analysis of its structure showed that the dihedral angle between the 2,4,6-trimethylbenzene rings was 90.2 ± 1.0°. We presume that this conformation is adopted because of the steric influence of the ortho-methyl groups and that it is effectively maintained in I.

A solution of the diazo compound (2×10^{-3} M) in isopentane/ether (1:1 v/v) was cooled to form a glass. After 20 s of irradiation at 5.8 K using a 1000-W mercury-xenon lamp, a strong triplet EPR spectrum was observed, which was analyzed in terms of D and E values[8,9] see Table I. D is a measure of the dipolar interaction between the unpaired electrons and hence of their average separation.[8] The measured value was less than that observed for most simple diarylcarbenes[11] but was still sufficiently large that the spectrum can be confidently assigned to I. E is a measure of the difference in the dipolar interaction along the x and y axes;[8] hence for most practical purposes E is zero when a molecule is linear. Nonzero values of E are a measure of the deviation from linearity when weighted by D.[8]

Table I. Values of D and E for Dimesitylcarbene in Various Matrices

matrix	temp, K	D, MHz	E, MHz
before annealing			
isopentane/ether	6	10 675 ± 100	375 ± 30
1,1-diphenylethylene	6	10 600 ± 100	348 ± 30
1,1-diphenylethylene	77	10 540 ± 60	355 ± 20
n-octane	77	10 550 ± 30	345 ± 10
after annealing			
isopentane/ether	77	10 380 ± 60	245 ± 20
1,1-diphenylethylene	77	10 480 ± 50	235 ± 15
2-methyltetrahydrofuran	77	10 460 ± 30	250 ± 10

Diphenylcarbene and essentially all substituted diphenylcarbenes have central C-C-C bond angles of ca. 150°.[10,11] Their D and E values are typically 12 000 and 580 MHz, respectively.[11] For dianthrylcarbene,[12] in which the aryl groups are orthogonal, D = 9020 MHz, indicating extensive delocalization of the unpaired electrons, and E = 0 MHz, which shows that it has a linear structure. The values of D and E for I (see table) show that its structure lies somewhere between these two extremes[13] and is therefore substantially closer to linearity than the structures of unhindered diarylcarbenes.

When the isopentane-ether glass was warmed to 77 K, there was a striking shift in the positions of the x and y lines,[8] which moved closer together, indicating a substantial reduction in E. Smaller shifts on the z lines showed that D had also diminished (see table). Similar changes occurred when diphenylethylene was used as host. At 77 K these samples showed D and E values that were similar to those observed at 5.8 K in isopentane-ether glasses. However, as the diphenylethylene samples were warmed to 184 K in 10 K increments, the x and y lines moved steadily closer together. Cooling the samples did not reverse this change. For dimesitylcarbene in 2-methyltetrahydrofuran at 77 K the lower values of D and E were observed without substantial annealing (table).

Changes of this kind but not of this magnitude have been observed for dianthrylcarbene.[12] They indicate that rigid matrices prevent the carbene from assuming its minimum-energy geometry and that it is only when such matrices are softened by annealing that relaxation to the preferred geometry takes place. The dramatic reduction in E suggests that in its relaxed geometry dimesitylcarbene has a structure that is quite close to linear.

Dimesitylcarbene was also found to be quite persistent in all of the matrices examined at 77 K. In particular, when formed from dimesityldiazomethane (10^{-5}M) in *n*-octane or 1,1-diphenylethylene glasses, it showed no sign of decay over a period of 4-5 h. By contrast, diphenylcarbene and fluoroenylidene need to be generated from high concentrations of diazo compound, ca. 0.1 M, presumably because these carbenes are long lived only when formed in microcrystallites of diazo compound.[14] Even under

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(1) Issued as NRCC publication No. 21123.

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(9) The spectra were analyzed by assuming $g_{xx} = g_{yy} = g_{zz} = 2.0025$ by analogy with diphenylcarbene.[10] When the spectra were solved by treating g as a variable, similar results were obtained for D and E, but the large spectral line widths, ca. 100 G, made an accurate determination of g impossible.

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(13) For a theoretical treatment of the relationship between D and E and the central C-C-C angle in carbenes see: Higuchi, J. *J. Chem. Phys.* **1963**, *39*, 1339.

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these conditions they are less persistent than dimesitylcarbene.[14]

The steric interactions of the ortho-methyl groups must have a profound effect on the structure of I. They force it to adopt a structure that is close to linear and presumably overhang the reactive site so that attack at solvent molecules is disfavored and intramolecular abstraction at a methyl group becomes a viable decay pathway.[2] Perhaps the most intriguing aspect of its chemistry is that unlike other diaryl carbenes I does not react to form an azine, even though this molecule is thermally and photochemically stable, but preferentially forms a sterically congested dimer (reactions 1 and 2). As was previously suggested,[2] azine formation should in principle proceed from the singlet state while dimer formation can take place in a triplet–triplet reaction.

Dimesitylcarbene has a geometry that effectively maximizes the triplet–singlet energy gap.[15] The steric interactions of the methyl groups will also disfavor ring rotations and reduction of the central C–C–C bond angle, which could provide a pathway for intersystem crossing from the triplet to singlet state, thus discriminating against azine formation. However, another intriguing possibility is that the steric influence of the methyl groups is so important that carbene molecule reactions require substantial activation energy, and as a consequence carbene–carbene combination becomes a significant reaction pathway. The kinetics for these reactions are currently under investigation.

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Registry No. I, 85236-86-8; dimesityldiazomethane, 61080-14-6.

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Triacridine Derivative: First DNA Tris-Intercalating Ligand

Graham J. Atwell, Werner Leupin, Simon J. Twigden, and William A. Denny*

Cancer Research Laboratory, School of Medicine
University of Auckland, Private Bag
Auckland, New Zealand

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In 1961 it was recognized[1] that the acridine derivative proflavine binds to double-stranded DNA primarily by intercalation of the aromatic chromophore between the base pairs.

In efforts to obtain compounds of higher DNA affinity for use both as possible antitumor agents[2,3] and as probes of ligand–DNA interactions,[4,5] several groups have investigated compounds containing two chromophores joined by various linker groups. These compounds generally show much greater DNA affinity than the corresponding single chromophores, and many examples have been shown by a variety of techniques[6] to be true DNA bis-intercalators.

We now report the synthesis of the triacridine derivative **1c** (Scheme I) together with the two model compounds **1a** and **1b**. A comparison of the DNA-binding behavior of the three compounds strongly indicates that **1c** is the first DNA tris-intercalating ligand. Acridine was chosen as the chromophore because of its proven[7] propensity to bind to DNA in the intercalative mode. To keep unfavorable entropic effects to a minimum, the spacing distance between the chromophore needed to be the shortest that would permit them all to intercalate.

Scheme I

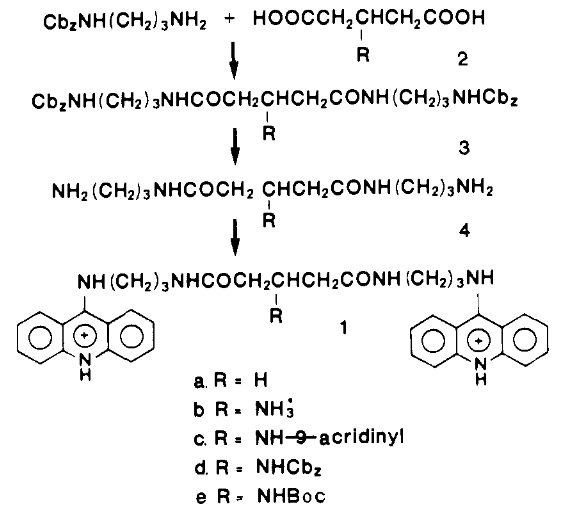

Table I. Interaction of Compounds **1a**-**c** with DNA

	UV-vis absorption[a]				
	free ligand		bound ligand		
compd	λ, nm	ε, M^{-1} cm^{-1}	λ, nm	ε, M^{-1} cm^{-1}	r^b
1a	437	11100	440	8600	0.0365
	413	13600	417	9800	
	267	60300			
1b	437	11700	440	9300	0.0409
	413	15000	417	10500	
	259	63400			
1c	435	15600	440	13700	0.0265
	412	21300	417	16600	
	257	108000			

[a] In 0.01 M SHE buffer, pH 7.0, $T = 25$ °C; [ligand] = 10^{-5} M; D/P ratio = 1/100; calf thymus DNA. [b] Ligand per phosphate ratio in 0.01 M SHE buffer at the equivalence point of the viscometric titration of PML-21 DNA; $T = 25.3$ °C; [DNA] = 1.59×10^{-4} M (P). Under the same condition, *r* values were determined for ethidium bromide (0.0464), 9-aminoacridine (0.0812), and 9-(ethylamino)acridine (0.0770). These values are not corrected for free ligand, but the error thus introduced is less than 10%.

From the above considerations, the linker chain **4b** was chosen. The two amide linkages provide excellent water solubility for the resulting ligand (**1c**), and Courtauld models of the side chain in the fully staggered conformation indicate a fairly constrained structure with the three amine groups positioned on the same side of the molecule, providing interchromophore distances of about 7 Å. Reaction of 3-(*N*-benzyloxycarbonyl)aminoglutaric acid (**2d**[8]) with *N*-(benzyloxycarbonyl)propane-1,3-diamine and diethyl phosphorocyanidate[9] gave the tris(carbobenzyloxy) derivative **3d**. Hydrogenolysis of the protective groups and usual coupling of the resulting triamine **4b** with 9-chloroacridine gave the triacridine trihydrochloride **1c** as a yellow, crystalline water-soluble solid. The synthetic scheme offers considerable scope for variation; thus use of glutaric acid provided the diacridine **1a**, while employment of the Boc-protected aminoglutaric acid **2e** gave the triply charged diacridine **1b**. Reaction of the last compound with 1 equiv of 9-chloroacridine converted it to the triacridine **1a**.[10]

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