

Photochemistry of Crystalline Chlorodiazirines: The Influence of Conformational Disorder and Intermolecular $\text{Cl}\cdots\text{N}=\text{N}$ Interactions on the Solid-State Reactivity of Singlet Chlorocarbenes[†]

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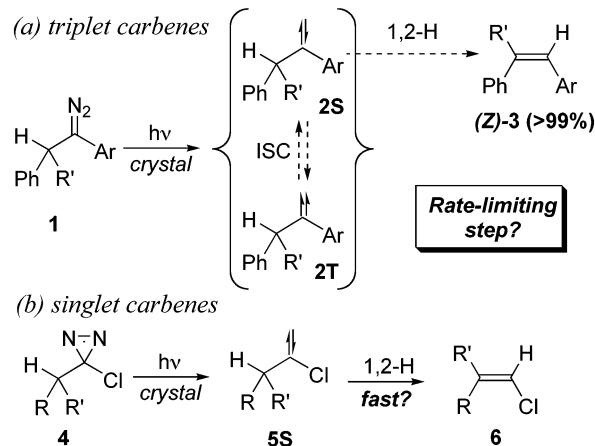
A photochemical study was carried out with 3-substituted 3-chlorodiazirines with 4-biphenyl- (**4a**), (4-biphenyl)-methyl- (**4b**), 2-(4-biphenyl)ethyl- (**4c**), and 1,1-dimethyl-1-(4-biphenyl)methyl (**4d**) substituents. The chlorodiazirines were prepared from the corresponding amidines (**7**) by a procedure involving oxidation with *tert*-butyl hypochlorite under phase-transfer catalysis. The crystalline nature of **4a–d** was established by differential scanning calorimetric analysis, which revealed melting endotherms prior to thermal decomposition. Photochemical results in crystalline solids were analogous to those observed in solution, and the products were analyzed in terms of the corresponding singlet-state chlorocarbene intermediates (**5a–d**). Irradiation of **4a** in solution and in crystals resulted in formation of azine **9a** by reaction of carbene **5a** with its precursor. Equally selective, diazirine **4d** gave alkene **6d** as the only product by a 1,2-Ph migration from carbene **5d**. In contrast, irradiation of compounds **4b** and **4c** resulted in formation of two alkenes by 1,2-H shifts and formation of azines by reactions of the carbenes with their precursors. The low selectivity of **4b** was rationalized in terms of structural data from single-crystal X-ray diffraction analysis, which revealed two disordered diazirine conformers and close $\text{Cl}\cdots\text{N}$ contacts between adjacent molecules. Rapid conformational equilibration in the solid state was also suggested by solid-state ¹³C CPMAS NMR. Similar structural effects are also postulated to account for the solid-state reactivity of **4c**.

1. Introduction

We have shown that triplet arylalkyl carbenes **2T** generated in crystals of their arylalkyldiazo precursors **1** undergo 1,2-H shifts from their thermally populated singlet states **2S** with remarkably high yields and stereoselectivities (Scheme 1a).¹ Although nanosecond lifetimes have been measured in solution for several 1,2-diphenylethylidenes (**2**),^{1d} kinetic estimates in crystals reveal time constants that range from hours at 77 K to several seconds at 273 K. Since the photochemical formation of the carbene **2** in the solid state should be very fast, slow reaction rates may be due to crystal effects on the rates of intersystem crossing or on the rate of the 1,2-H shift. To discern which of these alternatives, if any, may be correct, we decided to explore the solid-state reactivity of similar systems with carbenes that have a singlet ground state (Scheme 1b).

Given the large amount of mechanistic information available from solution and matrix isolation studies on singlet-state halocarbenes,^{2,3} we chose to study the reactivity of chlorocarbenes **5S** in crystals of 3-chlorodiazirines **4**. On the basis of our previous experience with crystalline derivatives of related compounds,¹ we set out to prepare a series of chlorodiazirines with a 4-biphenyl moiety (**4a–d**, Chart 1)⁴ and to investigate their photochemistry in solution and in the solid state. When very low yields of **4a–d** were obtained using the standard Graham oxidation procedure,⁵ we developed a simple modification based on the use of a phase-transfer catalyst (PTC) and *tert*-butyl hypochlorite. Pure solid samples were characterized

SCHEME 1



by differential scanning calorimetry and, in the case of **4b**, by X-ray diffraction and solid-state NMR. Reactions in the solid state are consistent with the formation of singlet carbenes that react under the constraints imposed by the crystal lattice of the chlorodiazirine precursor. However, partial product formation from the excited-state chlorodiazirines^{2f,34} cannot be ruled out from the results of this study.

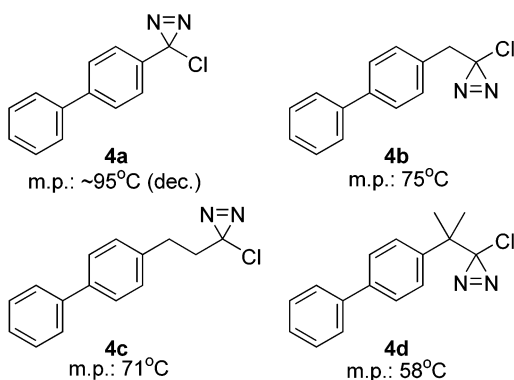
2. Results

2.1. Synthesis of Chlorodiazirines. Our initial attempts toward the synthesis of **4b** were based on the hypochlorite oxidation of amidines reported by Graham,⁵ as shown by the sequence of reactions in Scheme 2. However, while amidine hydrochloride **7b** ($\text{R} = \text{PhPhCH}_2$) was obtained in good yields

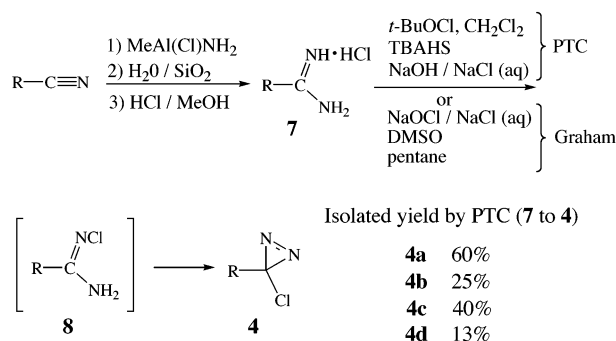
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CHART 1



SCHEME 2



from the corresponding nitrile,⁶ chlorodiazirine **4b** was obtained in 0–5% yields from **7b** upon oxidation with sodium hypochlorite in dimethyl sulfoxide (DMSO) and pentane. The major product of this reaction was chloroamidine **8b**, which precipitated out of the reaction mixture in 60% yield along with several other unidentified components. Given that chloroamidines are intermediates in the oxidation mechanism (Scheme 2),^{5,7} we reasoned that low yields in the case of **4b** may reflect the low solubility of **8b**. At the same time, the oxidation efficiency may be diminished by rapid reaction of hypochlorite with DMSO,⁸ which was easily established by iodometric titration.

To increase the yield of the desired chlorodiazirine, we explored experimental factors expected to increase the solution concentrations of **8b**, the oxidant, and chloride ion. We showed that intermediate **8b** is very soluble in pyridine, dimethylformamide (DMF), and DMSO and somewhat less soluble in dioxane, MeCN, and MeOH. In all cases, the solubility diminished when the aqueous oxidant and chloride ion were added. We also established that MeOH, DMF, MeCN, and pyridine react with hypochlorite more slowly than DMSO. With these facts in mind, we tested the reaction using each of those solvents with the ratio of solvent to water adjusted to obtain the highest concentration of **8b**. Additionally, due to their greater solubility, LiOCl and LiCl were used in place of the corresponding sodium salts. Unfortunately, these changes did not increase the yield of **4b**.⁹

To facilitate the co-dissolution of the hydrophobic substrate and the ionic reagents, we decided to explore a microheterogeneous system consisting of an aqueous solution, a water-immiscible organic solvent, and a PTC. In our first trial, we used conditions similar to those employed previously for the oxidation of alcohols and amines by NaOCl in a biphasic system using tetrabutylammonium hydrogen sulfate (TBAHS) as a PTC.¹⁰ Initially, **8b** was placed in a mixture of CH₂Cl₂ and aqueous NaOCl (1.6 M) saturated with NaCl and containing 20 mol % TBAHS. The reaction was worked up after 12 h,

TABLE 1: Yields of 3-Substituted 3-Chlorodiazirine in Side-by-Side Reactions by Use of a Phase-Transfer Catalyst (PTC) and by Standard Graham Oxidation^{a,b}

3-substituent	PTC (%)	Graham (%)
1-biphenylmethyl (4b)	35	~1
1-naphthylmethyl (4e)	14	~1 ^c
benzyl (4f)	47	11

^a Reactions were carried out to completion. ^b Yields determined by ¹H NMR using an internal standard. ^c We were unable to reproduce a yield of 15% reported in ref 15.

when most of the starting material had reacted. Analysis by ¹H NMR showed that diazirine **4b** was a minor constituent of the reaction mixture. Hoping to increase the amount of oxidant present in the organic phase, we replaced NaOCl with *tert*-butyl hypochlorite (*t*-BuOCl). Under this variation, **8b** was dissolved in a biphasic system consisting of CH₂Cl₂ and 1.0 M NaOH in brine containing 20 mol % TBAHS. To this mixture was slowly added a solution of *t*-BuOCl in CH₂Cl₂. After only 1 h, **8b** disappeared, and ¹H NMR analysis of the crude product mixture showed a significant proportion of diazirine **4b**. Control experiments demonstrated that the presence of TBAHS, base, and chloride ion in the aqueous phase are all necessary for optimum yields.

Optimal reaction conditions determined with **7b**¹¹ using the PTC were subsequently applied to the synthesis of chlorodiazirines **4a–d** (Scheme 2). Although product yields improved substantially, those of compounds **4b** and **4d** remained relatively modest (25 and 13%, respectively). Knowing that low yields (5–22%) have been reported for less hydrophobic benzylic diazirines using the Graham procedure,^{12–14} it was of interest to carry out a side-by-side comparison of the two methods. Along with the synthesis of **4b**, we decided to test the formation of 3-(1-naphthylmethyl)-3-chlorodiazirine (**4e**) and 3-benzyl-3-chlorodiazirine (**4f**), both of which have been previously reported (Table 1). Since there are slight differences in the Graham oxidation reported for those compounds, we followed precisely the procedure reported for the synthesis of 3-(1-naphthylmethyl)-3-chlorodiazirine.¹⁵ Reaction yields in Table 1, measured by ¹H NMR using an internal standard, show that experimental conditions using the PTC method result in significantly higher yields than those with the traditional method. Yield improvement from ca. 1% using the Graham method to as much as 35% by the PTC method in the case of **4b** suggest that the modified procedure should be broadly applicable to compounds that are highly hydrophobic and with large molecular weights such as those required for our studies in nonpolar molecular crystals.

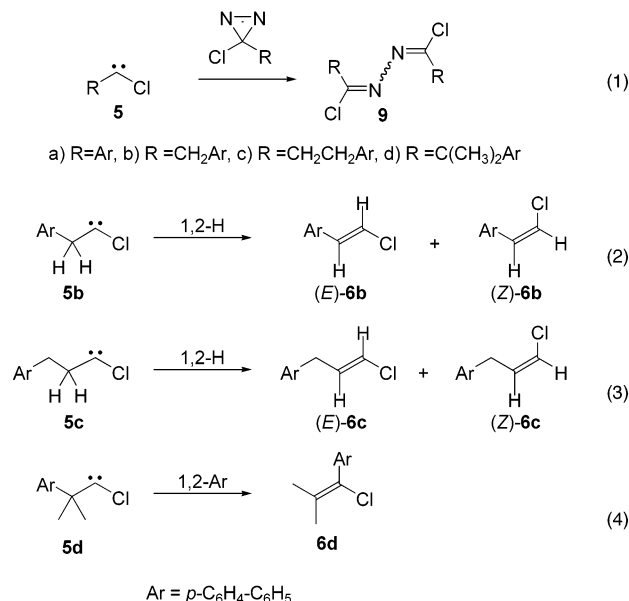
2.2. Photochemistry in Solution and in the Solid State.

Compounds **4a–d** were purified by column chromatography and isolated as white solids with microcrystalline appearance. Despite the explosive character associated with chlorodiazirines, small quantities (20–100 mg) were easy to handle and stable for months when protected from light at –10 °C.¹⁶ Dilute benzene solutions and polycrystalline samples of **4a–d** were irradiated with a 400 W medium pressure with a Hanovia lamp using a λ > 360 nm glass filter. The extent of conversion and the identity of the photoproducts were determined by ¹H NMR (Table 2). Solution photolyses carried out in argon-purged benzene at ambient temperature for 2 h gave high conversion values (88–99%). Control experiments in solution showed that photoisomerization of the isomeric alkenes does not occur under the reaction conditions. Photolyses in the solid state for 30 min to 6 h gave conversions between 26 and 99%, depending on the sample. Finely powdered samples were placed between

TABLE 2: Product Distribution Obtained by Photolysis of Chlorodiazirines 4a–d at 298 K^a

	conditions	conv (%)	normalized product distribution (%)		
			(Z)- 6	(E)- 6	9
4a	C ₆ D ₆	>95			100
	solid	>95			100
4b	C ₆ D ₆	88	21 (15) ^b	79 (85) ^b	0
	solid	26	48	38	14
	solid	65	41	37	22
4c	C ₆ D ₆	97	74 (68) ^b	26 (32) ^b	0
	solid	32	78	12	10
	solid	90	52	11	37
4d	C ₆ D ₆	96	100		
	solid	99	100		

^a Normalized product yields determined by ¹H NMR. ^b Results in cyclohexane as reported in ref 19a.

SCHEME 3

microscope slides, exposed to filtered UV light, and dissolved in CDCl₃ for analysis. Signals corresponding to the biphenyl alkenes (Z)-**6b** and (E)-**6b** were very similar to those previously reported in the literature for the phenyl analogues and were confirmed by comparison to those of authentic samples prepared independently. Signals corresponding to (Z)-**6c** and (E)-**6c** were assigned by analogy to those of (Z)-**6b** and (E)-**6b**. Small amounts of azines **9a–c** and alkene **6d** were isolated from small scale photolysis of the corresponding diazirines and were characterized by conventional methods.

The results of solution photolyses in Table 1 were consistent with literature reports for analogous compounds with a benzyl rather than 4-phenylbenzyl substituents and can be understood in terms of the expected carbene intermediates (Scheme 3).^{2,12–14,17–19} In inert solvents and in the absence of trapping reagents, biphenylchlorocarbene **5a** reacts with its own precursor to form azine **9a** as the only observable product (Scheme 3, eq 1).^{17,20} In contrast, halocarbenes **5b–d** have migrating α-groups that undergo fast intramolecular rearrangements. Chlorocarbenes **5b,c** give rise to alkenes (Z)-**6** and (E)-**6** by facile 1,2-H shifts (Scheme 3, eqs 2 and 3).^{12,14,18–20} and carbene **5d** gives rise to **6d** by an efficient 1,2-Ph migration (eq 4).¹³

Reactions in the solid state at 298 K differed from those in solution only in the cases of **4b,c**. The reactions of **4a,d** were as clean in crystals as in solution, yielding azine **9a** and alkene **6d**, respectively. Product formation in crystals of **4b,c** was more

TABLE 3: Product Distribution from Photolysis of Chlorodiazirine 4b in the Solid State between 298 and 66 K

temp (K)	conv (%)	product distribution ^a (%)		
		Z-alkene	E-alkene	azine
298	95	38	44	18
298	77	35	46	19
160	63	40	39	21
135	72	43	47	10
115	70	51	44	6
100	73	55	41	4
66	44	59	39	2

^a Product distribution was determined by ¹H NMR. The estimated integration error is ±5%.

complex than in solution and changed slightly as a function of reaction progress. In the case of **4b**, the ratio of (Z)-**6b** to (E)-**6b** reversed from 21:79 in solution to 48:38 in the solid state. The ratio of (Z)-**6c** to (E)-**6c** increased slightly from 74:26 in solution to 78:12 in the solid state. Reactions carried out to higher conversion values in crystals showed small changes in the (Z):(E) ratios with an increase in the yield of azine.

2.3. Variable Temperature Photolysis in Crystals of 4b.

It is possible that formation of azines and two 4-phenyl-β-chlorostyrene isomers will depress the melting points of **4b,c** so that reaction at ambient temperature may occur in liquid phases. To document this as the possible origin of the low selectivity observed, we investigated crystals of chlorodiazirine **4b** in a series of photochemical experiments carried out between 298 and 66 K. The reactions reported in Table 3 were carried out with films prepared with 3 mg of microcrystals spread between two quartz plates, placed in a cryostat cooled with N₂ gas, and irradiated with the filtered output (λ > 360 nm) of a 1000 W Hg–Xe lamp. Photolyses carried out with this setup for 60 and 30 min at 298 K gave 95 and 77% conversion, respectively. Reactions carried out for 1 h at 160 K and below gave only small variations on the extent conversion, which was close to 70% in most cases. The relatively small changes in reaction selectivity as a function of temperature between 66 and 130 K refute the possibility of melting as an explanation for the low selectivity in crystals of **4b**. The most significant change as a function of temperature involves the relative yields of the *cis*-1,2-H product (Z)-**6b** and azine **9b**. It may be noted that small changes in reaction selectivity and product yields over a very large temperature range are a clear indication of processes that occur with very small differences in activation energies and low absolute activation energy values.

2.4. X-ray Analysis of Diazirine 4b. Single crystals of 3-chlorodiazirines **4a,c,d** have been difficult to obtain.^{15,21} However, thin plates of **4b** with reasonable diffraction quality were obtained by slow solvent evaporation from pentane solutions kept at −10 °C. Diffraction data were collected at 100 K, and the structure of **4b** was solved in the monoclinic space group *P*₂₁/*c* with only one independent molecule per asymmetric unit.²² The molecular structure of **4b** is characterized by a planar biphenyl group with the chlorodiazirine being orthogonal to the aromatic plane, as described by a dihedral angle C(1)–C(2)–C(3)–C(4) of 93° (Figure 2a,b). The packing structure of **4b** has biphenyl and diazirine groups segregated in layers that take advantage of aromatic face-to-edge interactions and Cl⋯N interactions²³ (Figure 2, bottom). However, as illustrated in Figure 2, the three-membered ring of chlorodiazirine **4b** crystallizes conformationally disordered with two rotamers having 75:25 occupancies. The best refinement model gave R₁ = 0.054 for reflections with *I* > 2σ(*I*) and wR₂ = 0.1588 for all reflection data. The molecular structures were

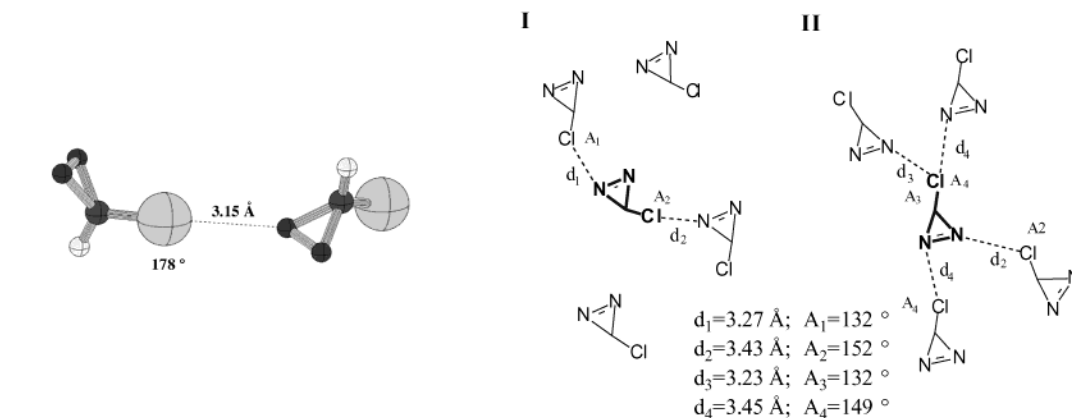


Figure 3. (Left) Structure of the HF 3-21G* optimized C–Cl \cdots N interaction in 3-chlorodiazirine. (Right) Schematic representation from the crystal structure of chlorodiazirine **4b**, illustrating close C–Cl \cdots N interactions with $d_{\text{Cl}\cdots\text{N}} < 3.5 \text{ \AA}$ for a reference molecule (boldface) shown in two possible orientations (I and II). In arrangement I, all the C–Cl bonds point down and only two short C–Cl \cdots N contacts are possible. In arrangement II, the C–Cl bonds point up and four C–Cl \cdots N close contacts are possible.

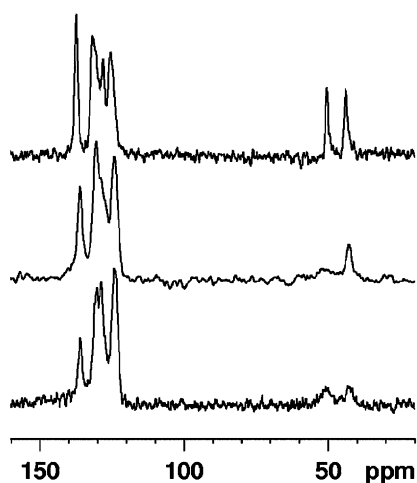


Figure 4. Solid-state CPMAS ^{13}C NMR spectra of **4b** obtained at 298 (top) and at 133 K (middle). The spectrum at the bottom was obtained at 133 K by direct polarization (Bloch decay).

occurs in the fast exchange limit to give a single average peak. To explore the latter, we measured a series of ^{13}C NMR spectra as a function of temperature between 298 and 133 K. Illustrated in Figure 4 are the spectra measured at 298 (top) and at 133 K (middle) using the CPMAS sequence. The bottom spectrum was measured at 133 K without cross-polarization but with high-power decoupling and magic angle spinning.²⁸ Spectra collected down to 173 K (not shown) resemble very closely the spectrum at 298 K, showing no changes over a 125 K range. However, as illustrated by the middle spectrum in Figure 4, there was a clear change in the CPMAS spectrum at 133 K, which is near the experimental limit of our temperature control. The signal assigned to the chlorodiazirine carbon at 50 ppm almost disappears at the baseline. One possible explanation would be that 133 K may be near the coalescence temperature so that conformational equilibration has slowed toward the slow-exchange regime of conformers with distinguishable chemical shifts.³² Although this can only be confirmed with measurements at lower temperatures, alternative interpretations based on the effects of conformational motions on the cross-polarization sequence can be easily tested without changing the temperature. As shown on the bottom spectrum in Figure 4, a ^{13}C NMR spectrum acquired by direct excitation and high-power decoupling (Bloch decay) restores the intensity of the diazirine carbon relative to that of the benzylic carbon. This result discounts an explanation based on signal coalescence (splitting) and suggests

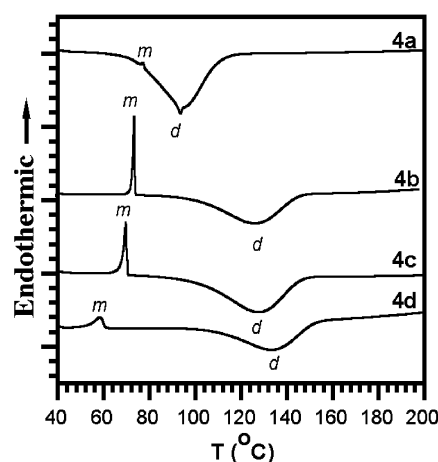


Figure 5. DSC curves for **4a–d** illustrating melting followed by exothermic denitrogenation (scanning rate $5^\circ\text{C}/\text{min}$).

a mechanism based on relaxation processes within the spin-locking field of the cross-polarization experiment. It is known that molecular motions in the $10^3\text{--}10^4 \text{ s}^{-1}$ dynamic range can interfere with cross-polarization by diminishing the magnitude of the $^1\text{H}\text{--}^{13}\text{C}$ dipolar coupling and by facilitating the decay of the spin-locked magnetization via a spin–lattice relaxation ($T_1\rho$) in the rotating frame.^{30b} This interpretation is consistent with the dynamic behavior of symmetric groups such as methyl-, *tert*-butyl-, adamantyl-, etc., which can undergo rapid molecular reorientations in the solid state.²⁷

2.6. Differential Scanning Calorimetric Analysis. Although we were unable to grow X-ray quality crystals of compounds **4a,c,d**, we were able to establish their crystallinity by differential scanning calorimetry (DSC).³³ As shown by the thermograms of **4a–d** in Figure 5, an endothermic peak was assigned to melting (*m*) and a broad exothermic transition to thermal denitrogenation and reaction (*d*). In the case of **4a**, a broad decomposition peak (*d*) centered at ca. 90°C overlaps with a weak melting peak at 77°C (*m*). The thermograms of compounds **4b–d** revealed melting endotherms between 58 and 75°C and the onset of decomposition starting at $90\text{--}100^\circ\text{C}$. A sharper transition for the melting of **4b** is consistent with its higher crystallinity.

3. Discussion

The photochemical results with biphenyl-substituted chlorodiazirines **4a–d** in dilute benzene solutions are very similar

to those reported in the literature for the phenyl analogues, where singlet chlorocarbenes have been detected by laser flash photolysis with the pyridine ylide method.^{2e,34} The analogous results observed in crystals suggest the formation of the same reactive intermediates.

Photoreactions in diazirine crystals proceed smoothly and are relatively clean. Aryldiazirine **4a** gives only azine **9a** by reaction of carbene **5a** with a neighboring diazirine molecule^{4,17} and (dimethylbenzyl)chlorodiazirine **4d** gives the α -chlorostyrene **6d** by a selective 1,2-Ph migration in the singlet state of **5d**.¹³ The lack of azine formation in crystals of **4d** implies a very efficient solid-state 1,2-Ph shift, a disfavored intermolecular reaction, or a combination of the two. Unfortunately, we were not able to grow single crystals for X-ray analysis to determine whether the formation of azines is structurally feasible.

In contrast to **4d**, reaction selectivities in crystals of benzylic diazirines **4b,c** were significantly lower with concurrent 1,2-H shifts and bimolecular azine formation. While reactions in crystals tend to be significantly more selective than analogous reactions in solution, exceptions occur for reactions that occur at defect sites, when product accumulation causes a deterioration of the crystal lattice, when microscopic liquid phases occur by depression of the melting point or in crystals that are disordered.³⁵ Low selectivities at low conversion values and at very low temperatures in the case of **4b** are in agreement with the disordered and packing arrangement shown by X-ray analysis, and a similar explanation is likely in the case of diazirine **4c**.

3.1. Azine Formation. Azines form by reaction of singlet carbenes with their nitrogenated precursors in a near-diffusion-controlled process.^{20,36} Azine formation in solution becomes important in the absence of alternative reactions, when very high precursor concentrations are used or when thermally activated rearrangements are slowed at low temperatures.^{17,18a,20} The formation of azines **9b,c** in crystals of **4b,c** was not anticipated. Since changes in size and volume upon 1,2-H shifts are relatively small, we expected solid-state rearrangements at ambient temperature to be nearly as fast as in solution. The rate constants for 1,2-H shifts of benzylic³⁷ and secondary hydrogens³⁸ are $(6.7\text{--}5.9) \times 10^7 \text{ s}^{-1}$ for analogous carbenes, suggesting that molecular displacement required for bimolecular azine formation should be unable to compete with the rigid environment of crystalline solids. Thus, barring unexpectedly slow 1,2-H shifts in crystals, the concurrent formation of azines and alkenes in crystals of **4b,c** implies a very favorable predisposition for the bimolecular reaction.³⁹

The formation of azine **9b** in crystals of diazirine **4b** can be easily rationalized upon inspection of the crystal structure. Although the crystallographic disorder in **4b** precludes a rigorous geometric analysis, the crystal structure reveals diazirine nearest neighbors within distances and orientations that favor the reaction (Figures 3 and 6). It is expected that formation of azine **9b** will proceed by denitrogenation of a diazirine molecule followed by reaction between the resulting singlet carbene and a close neighbor in the crystal. The distance between the diazirine carbon of one molecule and a diazirine nitrogen of its closest neighbor is only 3.20 Å (Figure 6). A computational transformation of nearby diazirine neighbors into the minimized structure of the azine product can be carried out with no significant displacement of either biphenyl group (Figure 6, bottom). The distance between the diazirine carbons changes from 3.88 Å in the putative reactants to 3.56 Å between the corresponding carbon atoms in the product. It is interesting to note that formation of an intermediate ylide²⁰ may be possible. Calculations suggest the carbene-carbon and diazirine-nitrogen

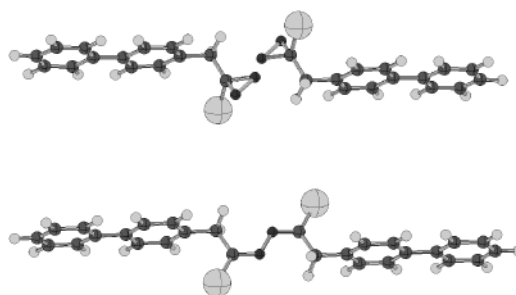


Figure 6. (Top) Neighboring molecules of diazirine **4b** shown in one of the two disordered conformers present in the crystal lattice. (Bottom) Hypothetical structure of azine **9b** derived from the structure of the dimer shown on top by assuming a least motion process. The top structures were taken from the X-ray coordinates, and the bottom one was derived directly from the one above followed by minimization with the AM1 method (constraining only the planarity of the biphenyl group).

to be at a distance of 1.3 Å in the methylene-diazirine ylide.^{20b} Although this is much shorter than the 3.20 Å between the corresponding atoms in the diazirine crystal, small molecular displacements are known to occur in many reactions, making the future detection and analysis of an ylide plausible.

3.2. Singlet-State 1,2-H Shift. In addition to 1,2-H shifts from singlet carbenes, it has been suggested that formation of chloroalkenes may also occur by a reaction involving concerted N₂ elimination and 1,2-H migration from the excited-state chlorodiazirine precursors.^{2f,34} Although this pathway was proposed to account for ca. 26% of the chlorostyrene formed in the case of benzylchlorodiazirine in solution,^{18d} product analysis offers no information which may reveal whether a similar pathway may contribute in the solid-state reactions of compounds **3b,c**. With regard to the carbene rearrangement, it is known that 1,2-H shifts occur from conformations where the σ bond of the migrating hydrogen is parallel to the empty p-orbital in sp²-hybridized singlet carbene (Scheme 4). The transition state is characterized by displacement of the hydrogen across the forming double bond and by planarization of the α -carbon.^{19b,40,41} As shown in Scheme 4, two alkene geometric isomers arise from syn- and anti-conformations of the carbene intermediate.^{18,39,40}

The stereoselectivity of the rearrangement is influenced by the population of the carbene conformers, by whether they can equilibrate and by their individual rate constants.^{20,36,40,42} A flat conformational profile calculated for rotation about the benzylic-diazirine carbon-carbon bond in **4b** suggests that there should be very small, if any, conformational bias in the precursor ($E_{\text{anti}} \approx E_{\text{syn}}$). Similarly, no conformational preference is expected in the carbene.²⁶ Recent computational studies with several chlorocarbenes by Keating et al. using B3LYP/6-31G* structural optimizations with zero point energies revealed very close syn- and anti-carbene conformers.^{40,43} Differences in conformational and transition-state energies for benzyl chlorocarbene, an excellent model for the biphenyl analogue **5b**, are illustrated in Figure 7. The difference calculated between the lowest energy anti-conformer and a near-lying syn-structure in BnCCl was only 0.7 kcal/mol. Cis- and trans-transition states (*cis*- and *trans*-TS) for 1,2-H shifts in benzyl chlorocarbene obtained by the same method were 8.8 and 6.8 kcal/mol above the syn- and anti-conformers, respectively, in agreement with reaction stereoselectivities in solution where a small preference for the (*E*)-alkene (*trans*-TS) in BnCCl is observed.¹⁸

It seems clear that the lack of solid-state selectivity observed in the 1,2-H shift of **4b**, and very likely **4c**, is controlled by the

SCHEME 4

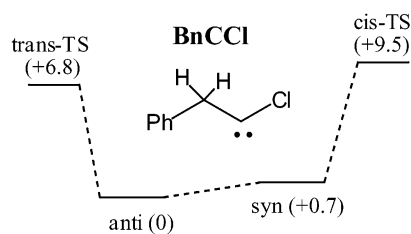
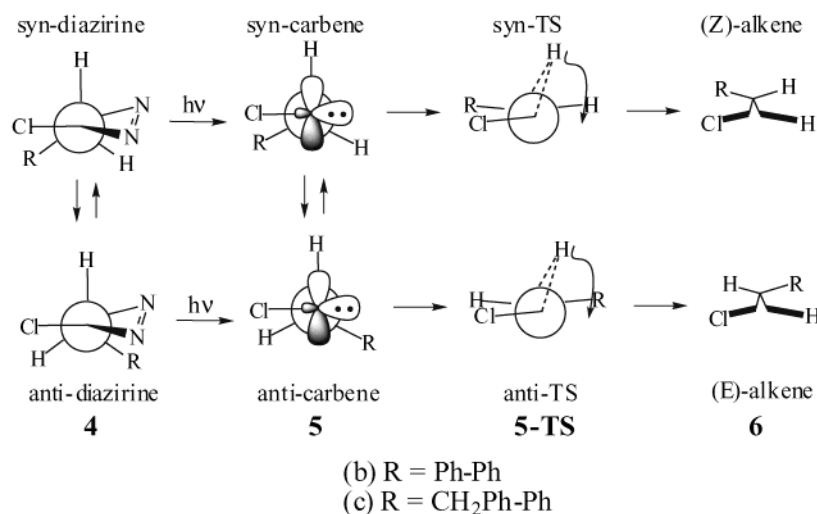


Figure 7. Relative B3LYP/6-31G* energies (kcal/mol; zpe corrected) for the syn- and anti-conformers of benzyl chlorocarbene, which can be used as a model for compound **5b**. Data taken from ref 40a.

structural disorder and conformational dynamics present in their crystals. Photolysis of crystalline **4b** at 298 K over a wide range of conversion values and reactions carried out at very low temperatures, where melting is unlikely, are consistent with results determined by the structure of the crystal. While each of the two diazirine conformers observed by X-ray diffraction could lead stereospecifically to each alkene isomer, the equilibration of carbene conformers in the solid state cannot be ruled out.

The effect of temperature on the solid-state reaction of **4b** is remarkably small. Matrix isolation studies by Wierlacher et al. suggest that 1,2-H shifts proceed rapidly by a tunneling mechanism even at 10–20 K.¹⁴ Assuming that formation of the carbene determines the formation of products in the solid state, the relatively small changes in chemical yields from 298 to 66 K suggest a nearly barrierless photodissociation of N₂ from the diazirine excited singlet state. A relatively small change in reaction selectivity from 298 to 66 K is characterized by a small increase in the yield of (Z)-**6b** and a small decrease in the yield of azine **9b**. These observations are consistent with modest changes in the relative populations and rates of conformational equilibration of diazirine and carbene conformers. Since azine formation in solution actually increases at lower temperatures^{18a} (indicating a smaller barrier than those of the 1,2-H shifts), a relatively slow decrease in the yield of azine in crystals is consistent with a small structural barrier in the product-determining step. A small increase in the yield of (Z)-**6b** may also reflect a structural bias. We propose that a rigid, or slowly equilibrating, conformation of the diazirine and carbene in the crystal should favor the formation of the (Z)-product due to Cl–C(1)–C(2)–C(3) dihedral angles that are less than 90°, when values of 180° are required to favor the (E)-isomer.

4. Conclusions

This work aims at understanding the factors that affect the rate of the 1,2-H shift of singlet carbenes in crystalline solids. As a first step, we have investigated the suitability of several biphenyl-substituted chlorodiazirines as crystalline precursors, including their preparation, crystallization, and reaction control. Having first identified serious synthetic problems associated with the low solubility of nonpolar reactants and intermediates under the conditions of the standard Graham procedure for the synthesis of 3-chlorodiazirines, we implemented a simple modification that proceeds in reasonable yields. We showed that the photochemical reactivity of biphenyl chlorocarbenes **5a–d** in solution is similar to that of their phenyl analogues. Reactions of biphenyl chlorocarbene **5a** and α,α -dimethyl-(4-phenyl)-benzyl chlorocarbene **5d** in crystals of their diazirine precursors proceeded in high yields to give azine **9a** and alkene **6d**, respectively, as the only products. In contrast, low selectivities were observed in reaction of carbenes **5b,c**, which give rise to azines **9b,c** along with (Z)- and (E)-alkenes **6b,c** from 1,2-H shifts. Product formation in the case of **5b** could be rationalized from the single-crystal X-ray structure of diazirine **4b**. Two chemically relevant features of the crystal structure are the rotational disorder of the chlorodiazirine group and the presence of an extended 2D network of nonbonded Cl–N interactions. Preliminary evidence of the dynamic nature of the rotational disorder was obtained by solid-state ¹³C NMR experiments, suggesting the need of a dynamic mechanistic model, rather than one derived from the static equilibrium structures available from X-ray diffraction. It appears that facile conformational equilibration of the chlorodiazirine, and perhaps also the carbene, results in formation of both (Z)-**6b** and (E)-**6b** from competing 1,2-H shifts. Similarly, the apparent mobility of adjacent diazirine groups leads to the facile formation of azine **9b** at ambient temperature and to its almost complete suppression below ca. 100 K. Work in progress suggests that conformational disorder and a network of nonbonded Cl–N interactions are frequent motifs in crystalline 3-chlorodiazirines.

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Supporting Information Available: General experimental procedures and spectral data of amidines **7b** and **8b**, diazirines

4a–d, alkenes 6b–d, and azines 9a–c, X-ray acquisition and refinement data for diazirine 4b, and contour diagram of the AM1 conformational surface of 4b. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References and Notes

- (1) (a) Garcia-Garibay, M. A.; Shin, S.; Sanrame, C. N. *Tetrahedron* **2000**, *56*, 6729. (b) Shin, S. H.; Cizmeciyan, D.; Keating, A. E.; Khan, S. I.; Garcia-Garibay, M. A. *J. Am. Chem. Soc.* **1997**, *119*, 1859. (c) Shin, S. H.; Constable, A. E.; Garcia-Garibay, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 7626. (d) Motschiedler, K. R.; Gudmundsdottir, A.; Toscano, J. P.; Platz, M. S.; Garcia-Garibay, M. A. *J. Org. Chem.* **1999**, *64*, 5139.
- (2) (a) Doyle, M. P. In *Chemistry of Diazirines*; Liu, M. T. H., Ed.; CRC Press: Boca Raton, FL, 1987; Vol. 2, Chapter 8, p 34. (b) Moss, R. A.; Turro, N. J. In *Kinetics and Spectroscopy of Carbenes and Biradicals*; Platz, M. S., Ed.; Plenum Press: New York, 1990; Chapter 7, p 213. (c) Moss, R. A. In *Advances in Carbene Chemistry*; Brinker, U. H., Ed.; JAI Press: Stamford, CT, 1994; Vol. 1, p 59. (d) Bonneau, R.; Liu, M. T. H. In *Advances in Carbene Chemistry*; Brinker, U. H., Ed.; JAI Press: Stamford, CT, 1998; Vol. 2, p 1. (e) Jackson, J. E.; Platz, M. S. *Advances in Carbene Chemistry*; Brinker, U. H., Ed.; JAI Press Inc.: New York, 1994; Vol. 1, pp 89–160. (f) Moss, R. A. *Pure Appl. Chem.* **1995**, *67*, 741–747.
- (3) (a) Sander, W.; Bucher, G.; Wierlacher, S. *Chem. Rev.* **1993**, *93*, 1583–1621. (b) Sheridan, R. S. *Org. Photochem.* **1987**, *8*, 159–248.
- (4) Compound 4a has been synthesized previously, and the reactivity of carbene 5a has been studied in solution. (a) Naito, I.; Nakamura, K.; Kumagai, T.; Oku, A.; Hori, K.; Matsuda, K.; Iwamura, H. *J. Phys. Chem. A* **1999**, *103*, 8187. (b) Naito, I.; Oku, A.; Fujiwara, Y.; Tanimoto, Y. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1051. (c) Naito, I.; Oku, A.; Otani, N.; Fujiwara, Y.; Tanimoto, Y. *J. Chem. Soc., Perkin Trans. 2* **1996**, 725.
- (5) (a) Graham, W. H. *J. Am. Chem. Soc.* **1965**, *87*, 4396. (b) Schmitz, E. In *Chemistry of Diazirines*; Liu, M. T. H., Ed.; CRC Press: Boca Raton, FL, 1987; Vol. 1, Chapter 3, 57.
- (6) (a) Moss, R. A.; Ma, W.; Merrer, D. C.; Xue, S. *Tetrahedron Lett.* **1995**, *36*, 8761. (b) Garigipati, R. S. *Tetrahedron Lett.* **1990**, *31*, 1969.
- (7) For mechanistic details of the Graham oxidation, see: (a) Moss, R. A.; Wlostowska, J.; Guo, W.; Fedorynski, M.; Springer, J. P.; Hirshfield, J. M. *J. Org. Chem.* **1981**, *46*, 5048. (b) Berneth, H.; Hüning, S. *Chem. Ber.* **1980**, *113*, 2040.
- (8) Hoyle, J. In *The Chemistry of Sulfones and Sulfoxides*; Patai, S.; Rapoport, Z.; Stirling, C., Eds.; Wiley: Chichester, U.K., 1988; Chapter 21, p 969.
- (9) For successful replacements of DMSO by MeOH see: (a) Rempala, P.; Sheridan, R. S. *J. Chem. Soc., Perkin Trans. 2* **1999**, 2257. (b) Yao, G.; Rempala, P.; Bashore, C.; Sheridan, R. S. *Tetrahedron Lett.* **1999**, *40*, 17.
- (10) Lee, G. A.; Freedman, H. H. *Tetrahedron Lett.* **1976**, 1641.
- (11) In a 50 mL round-bottom flask, 1 mmol of 7 was suspended in 12 mL of CH₂Cl₂ and 0.2 mmol of TBAHS was added. Under vigorous magnetic stirring, 12 mL of 1.0 M NaOH(aq) in saturated NaCl(aq) (from dilution of 5 M NaOH with brine) was added. A solution containing 0.5 mL of *t*-BuOCl in 2 mL of CH₂Cl₂ was then added over a period of ca. 45 min until the *N*-chloro intermediate 8 disappeared. The deeply colored biphasic emulsion was separated by decantation, and the aqueous layer was extracted once with CH₂Cl₂. The combined organic extract was dried over CaCl₂ and passed through a short column of silica gel with CH₂Cl₂ to remove the TBAHS. Purification by column chromatography (SiO₂, pentane) yielded the corresponding chlorodiazirine.
- (12) 3-Benzyl-3-chlorodiazirine was prepared in 22% yield: Liu, M. T. H.; Chishtu, N. H.; Tencer, M.; Tomioka, H.; Izawa, Y. *Tetrahedron* **1984**, *40*, 887.
- (13) 3-Chloro-3-(1-methyl-1-phenylethyl)diazirine was prepared in 5% yield: Liu, M. T. H. *J. Phys. Org. Chem.* **1993**, *6*, 696.
- (14) 3-Chloro-3-(phenyl-*ds*-methyl)diazirine was prepared in 12% yield: Wierlacher, S.; Sander, W.; Liu, M. T. H. *J. Am. Chem. Soc.* **1993**, *115*, 8943.
- (15) 3-(1-Naphthylmethyl)-3-chlorodiazirine is one of two 3-chlorodiazirines to have their X-ray structure determined (mp 41 °C). Linden, A.; Cameron, T. S.; Liu, M. T. H.; Anand, S. M. *J. Org. Chem.* **1988**, *53*, 1085.
- (16) Solid samples of compounds 4a–d do not show noticeable changes in the ¹H and ¹³C NMR spectra after months of storage (–10 °C).
- (17) (a) Liu, M. T. H.; Ramakrishnan, K. *Tetrahedron Lett.* **1977**, *36*, 3139. (b) Padwa, A.; Eastman, D. J. *J. Org. Chem.* **1969**, *34*, 2728.
- (18) Benzylchlorocarbenes: (a) Merrer, D. C.; Moss, R. A.; Liu, M. T. H.; Banks, J. T.; Ingold, K. U. *J. Org. Chem.* **1998**, *63*, 3010. (b) Bonneau, R.; Liu, M. T. H.; Kim, K. C.; Goodman, J. L. *J. Am. Chem. Soc.* **1996**, *118*, 3829. (c) Liu, M. T. H.; Bonneau, R. *J. Am. Chem. Soc.* **1990**, *112*, 3915. (d) Nigam, M.; Platz, M. S.; Sholwalter, B. M.; Toscano, J. P.; Johnson, R.; Abbot, S. C.; Kirchhoff, M. M. *J. Am. Chem. Soc.* **1998**, *120*, 8055–8059.
- (19) 2-Phenylethylchlorocarbene: (a) Tomioka, H.; Hayashi, N.; Sugiura, T.; Izawa, Y. *J. Chem. Soc., Chem. Commun.* **1986**, 1364. (b) Tomioka, H.; Sugiura, T.; Masumoto, Y.; Izawa, Y.; Inagaki, S.; Iwase, K. *J. Chem. Soc., Chem. Commun.* **1986**, 693.
- (20) (a) Bonneau, R.; Liu, M. T. H. *J. Phys. Chem. A* **2000**, *104*, 4115. (b) Shustov, G. V.; Liu, M. T. H.; Houk, K. N. *Can. J. Chem.* **1999**, *77*, 540.
- (21) 3-[(*p*-Nitrophenoxy)methyl]-3-chlorodiazirine is reported to be a very stable and highly crystalline solid. Its X-ray structure analysis, including electron density deformations, have been analyzed by: (a) Cameron, T. S.; Bakshi, P. K.; Borecka, B.; Liu, M. T. H. *J. Am. Chem. Soc.* **1992**, *114*, 1889. (b) Kwiatkowski, W.; Bakshi, P. K.; Cameron, T. S.; Liu, M. T. H. *J. Am. Chem. Soc.* **1994**, *116*, 5747.
- (22) Selected crystal data. For 4b: C₁₄H₁₁ClN₂, MW = 242.70, monoclinic, space group P2₁/c, *a* = 8.4274(12) Å, *b* = 5.6755(8) Å, *c* = 25.158(4) Å, β = 96.963(3)°, *V* = 1194.4(3) Å³, *Z* = 4, ρ_{calcd} = 1.350 Mg/m³, *F*(000) = 504, λ = 0.71073 Å, μ (Mo K α) = 0.296 mm^{–1}, *T* = 100(2) K, crystal size = 0.4 × 0.15 × 0.1 mm³. Of the 6572 reflections collected (1.63 ≤ θ ≤ 28.25°), 2588 [*R*(int) = 0.0275] were independent reflections; max/min residual electron density +397 and –383 e nm^{–3}, *R*1 = 0.0543 (*I* > 2 σ (*I*)) and *wR*2 = 0.1588 (all data).
- (23) (a) Metrangolo, P.; Resnati, G. *Chem. Eur. J.* **2001**, *7*, 2511. (b) Reddy, D. S.; Ovchinnikov, Y. E.; Shishkin, O. V.; Struchkov, Y. T.; Desiraju, G. R. *J. Am. Chem. Soc.* **1996**, *118*, 4085.
- (24) Keating, A. E.; Garcia-Garibay, M. A.; Houk, K. N. *J. Am. Chem. Soc.* **1997**, *119*, 10805. 10809.
- (25) (a) Wollrab, J. E.; Scharpen, L. H.; Douglas, M. J. *Chem. Phys.* **1969**, *51*, 1584. (b) Burkholder, D.; Jones, W. E.; Ling, K. W.; Wasson, J. S. *Theor. Chim. Acta* **1989**, *55*, 325.
- (26) A portion of the energy surface of diazirine 4b consisting of rotation about the Cl–C(1)–C(2)–C(3) and C(1)–C(2)–C(3)–C(4) dihedrals was investigated with the AM1 method using the Hyperchem package (Hyperchem Inc. Gainesville, FL). These calculations suggest a flat potential with a lowest energy anti-conformer having Cl–C(1)–C(2)–C(3) = 180° and close-lying syn-conformers with Cl–C(1)–C(2)–C(3) = ±75° that are only 1 kcal/mol above. These results are consistent with calculations reported in ref 14. Please see Supporting Information.
- (27) (a) Gavezzotti, A.; Simonetta, M. *Organic Solid State Chemistry*; Desiraju, G. R., Ed.; Elsevier: Netherlands, 1987; pp 391–432. (b) Gavezzotti, A. *Mol. Cryst. Liq. Cryst.* **1988**, *156A*, 25. (c) Gavezzotti, A.; Simonetta, M. *Stud. Org. Chem.* **1987**, *32*, 391.
- (28) Wash, P. L.; Ma, S.; Obst, U.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1999**, *121*, 7973.
- (29) Pines, A.; Gibby, M. G.; Waugh, J. S. *J. Chem. Phys.* **1973**, *59*, 569.
- (30) For some general reviews of the CPMAS experiment, please see: (a) Schaefer, J.; Stejskal, E. O. *Top. Carbon-13 NMR Spectrosc.* **1979**, *3*, 283. (b) Fyfe, C. A. *Solid State NMR for Chemists*; CFC Press: Guelph, Ontario, 1983. (c) Yannoni, C. S. *Acc. Chem. Res.* **1982**, *15*, 201. (d) Lyster, J. R.; Yannoni, C. S.; Fyfe, C. A. *Acc. Chem. Res.* **1982**, *15*, 208.
- (31) (a) Alemany, L. B.; Grant, D. M.; Alger, T. D.; Pugmire, R. J. *J. Am. Chem. Soc.* **1983**, *105*, 6697. (b) Opella, S. J.; Frey, M. J. *J. Am. Chem. Soc.* **1979**, *101*, 5854. (c) Opella, S. J.; Frey, M. H.; Cross, T. A. *J. Am. Chem. Soc.* **1979**, *101*, 5856.
- (32) Lyster, J. R.; Yannoni, C. S.; Fyfe, C. A. *Acc. Chem. Res.* **1982**, *15*, 208–216.
- (33) Hatakeyama, T.; Quinn, F. X. *Thermal Analysis: Fundamentals and Applications to Polymer Science*; Wiley: Chichester, U.K., 1994; Chapter 2, p 5, and Chapter 5, p 65.
- (34) Platz, M. S.; White, W. R.; Modarelli, D. A.; Celebi, S. *Res. Chem. Intermed.* **1994**, *20*, 175.
- (35) Keating, A. E.; Garcia-Garibay, M. A. *Molecular and Supramolecular Photochemistry*; Ramamurthy, V., Schanze, K. S., Eds.; Dekker: New York, 1998; Vol. 2, pp 195–248, and references therein.
- (36) (a) Liu, M. T. H.; Bonneau, R.; Wierlacher, S.; Sander, W. J. *Photochem. Photobiol. A* **1994**, *84*, 133.
- (37) Jackson, J. E.; Soundararajan, N.; White, W.; Liu, M. T. H.; Bonneau, R.; Platz, M. S. *J. Am. Chem. Soc.* **1989**, *111*, 6874.
- (38) LaVilla, J. A.; Goodman, J. L. *J. Am. Chem. Soc.* **1989**, *111*, 6877.
- (39) Studies with crystalline diphenyldiazomethane showed the first example of azine formation in crystals: Doetschman, D. C.; Hutchison, C. A., Jr. *J. Chem. Phys.* **1972**, *56*, 3964.
- (40) (a) Keating, A. E.; Garcia-Garibay, M. A.; Houk, K. N. *J. Phys. Chem.* **1998**, *102*, 8467. (b) Nickon, A. *Acc. Chem. Res.* **1993**, *26*, 84–89. (c) Sugiura, M. H.; Celebi, S.; Platz, M. S. *J. Am. Chem. Soc.* **1992**, *114*, 966–973. (d) Schaefer, H. F., III. *Acc. Chem. Res.* **1979**, *12*, 288–96.
- (41) Shustov, G. V.; Liu, M. T. H.; Rauk, A. *J. Phys. Chem. A* **1997**, *101*, 2509.
- (42) Tomioka, H.; Hayashi, N.; Izawa, Y.; Senthilnathan, V. P.; Platz, M. S. *J. Am. Chem. Soc.* **1983**, *105*, 5053.
- (43) Keating, A. E. *Computational Studies of Carbene Reactions*. Ph.D. Thesis, University of California, Los Angeles, 1998.