

# Lifetimes of Dialkylcarbocations Derived from Alkanediazonium Ions in Solution: Cyclohexadienyl Cations as Kinetic Probes for Cation Reactivity<sup>1</sup>

John Paul Pezacki,<sup>\*,†,‡,§</sup> Deepak Shukla,<sup>‡</sup> Janusz Lusztyk,<sup>‡</sup> and John Warkentin<sup>†</sup>

Contribution from the Department of Chemistry, McMaster University, Hamilton, Ontario, Canada L8S 4M1, and the Steacie Institute for Molecular Sciences, National Research Council of Canada, Ottawa, Ontario, Canada K1A 0R6

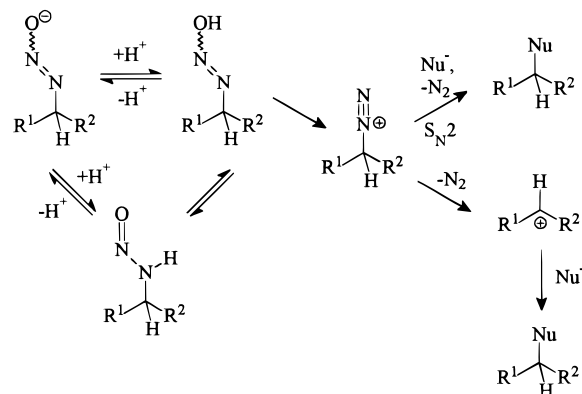
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**Abstract:** The first estimates of the lifetimes of the 2-propyl cation (**4a**), cyclobutonium ion (**4b**), cyclopropylethyl cation (**4c**), and 2-adamantyl cation (**4d**) in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), trifluoroethanol (TFE), and acetonitrile solvents have been determined using electrophilic aromatic addition to 1,3,5-trimethoxybenzene as a kinetic probe reaction in laser flash photolysis (LFP) experiments. The lifetimes ranged from ~100 ps to ~40 ns at 22 °C. Oxadiazoline precursors **1** were used to generate *sec*-dialkylcarbazones **2** by LFP which, in the presence of a proton source, give rise to *sec*-alkanediazonium ions **3** that lose N<sub>2</sub> rapidly to form carbocationic intermediates **4**. The cations were found to react with 1,3,5-trimethoxybenzene to form cyclohexadienyl cations. The latter were monitored by LFP. Stern–Volmer kinetics were used to determine lifetimes and rate constants for reactions of cations **4a–d**. Short lifetimes of **4a–d** imply that simple *sec*-alkanediazonium ions, from carcinogenic *N*-alkyl-*N*-nitrosamines, must be generated within contact distances of DNA through a preassociation mechanism in order to effect alkylation.

## Introduction

Diazonium ion intermediates have been of considerable interest since their discovery by Griess in 1861.<sup>2</sup> Diazoalkanes and their conjugate acids, diazonium ions, are important reactive intermediates which have been implicated in the carcinogenicity and mutagenicity of *N*-alkyl-*N*-nitroso compounds.<sup>3</sup> The carcinogenic properties of *N*-alkyl-*N*-nitrosamines were first recognized in the late 1960's.<sup>4</sup> There are several different classes of carcinogenic nitroso compounds including *N*-nitrosamines, *N*-nitrosamides, *N*-nitrosoureas, and *N*-nitro-*N*-nitrosoguanidines. In some cases, *N*-nitrosamines are hydroxylated enzymatically at one of the α-aminocarbons.<sup>5,6</sup> Decomposition of the resulting intermediates give rise to alkanediazoic acids. The (*E*)- and (*Z*)-isomers<sup>7</sup> of alkanediazoates and their conjugate acids have been shown to decompose in aqueous medium yielding alkanediazonium ions.<sup>8,9</sup> The resulting alkanediazonium ions then react with nucleophiles by either S<sub>N</sub>1 or S<sub>N</sub>2 pathways (Scheme

## Scheme 1



1).<sup>10,11</sup> Reactions with biological nucleophiles, including DNA, give rise to intracellular damage. Our interests lie in determining the lifetimes of the intermediates on the pathways to alkylation and relating them to possible mechanisms of DNA damage and carcinogenesis.

<sup>†</sup> McMaster University.

<sup>‡</sup> National Research Council of Canada.

<sup>§</sup> NRCC Visiting Scientist, 1996–1998. Present address: Department of Chemistry, University of Toronto, Toronto, Ont. e-mail address: jpezacki@chem.utoronto.ca.

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Methanediazonium ions<sup>8–12</sup> and simple primary alkanediazonium ions<sup>8–10,13</sup> react with nucleophiles by S<sub>N</sub>2 mechanisms. Theory suggests that loss of N<sub>2</sub> from primary alkanediazonium ions is endothermic.<sup>14,15</sup> The stereochemical investigation of nucleophilic substitution on optically active [1-<sup>2</sup>H]butanediazonium ion and [1-<sup>2</sup>H]-2-methylpropanediazonium ion showed that they undergo nucleophilic substitution by an S<sub>N</sub>2 pathway (complete inversion of configuration, >92% ee).<sup>13</sup> Furthermore,  $k_{\text{LiN}_3}/k_{\text{MeOH}}$  for 1-butanediazonium and 1-hexanediazonium ions are 17.6 and 18.4,<sup>16</sup> respectively, implying that primary alkanediazonium ions are more selective because they react via S<sub>N</sub>2 pathways.

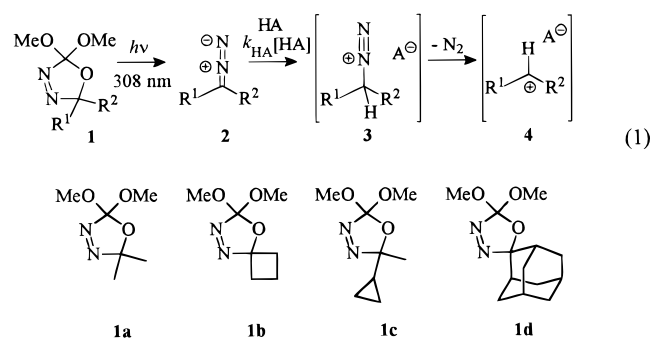
In contrast, secondary diazonium ions lose N<sub>2</sub> very rapidly and undergo reactions with nucleophiles via S<sub>N</sub>1 mechanisms.<sup>8–10,17</sup> The generation of simple aliphatic diazonium ions via protonation of the corresponding diazoalkane leads to diazonium ion-counter ion pairs. In the case of *sec*-alkanediazonium ions, N<sub>2</sub> dissociation occurs rapidly within these ion pairs giving rise to secondary carbocations.<sup>8–10</sup> A consequence of the diminished lifetimes of diazonium ions due to N<sub>2</sub> loss is that they alkylate via carbocation intermediates which, depending of their stability, will be less sensitive to the relative nucleophilicities of the incipient attacking groups than diazonium ions which react by a concerted mechanism.<sup>18</sup> Exceptions include 1-phenyl-2,2,2-trifluoroethanediazonium ion<sup>19</sup> and bis-(trifluoromethyl)methanediazonium ion<sup>20</sup> which have been observed at low temperatures by NMR in superacids, as well as 1-cyano-1-propanediazonium ion, which partitions between S<sub>N</sub>1 and S<sub>N</sub>2 mechanisms.<sup>21</sup>

To follow carbocation reactions by direct kinetic methods such as LFP, the cations require a UV-visible chromophore in a useful (monitorable) region of the spectrum. In the absence of such a chromophore, or a suitable photochemical precursor,<sup>22</sup> indirect methods based either on competition kinetics<sup>23</sup> or on a kinetic probe reaction<sup>24,25</sup> are required. Herein we report that 1,3,5-trimethoxybenzene reacts with highly electrophilic carbocations to yield substituted cyclohexadienyl cations which

are easily monitored by UV-LFP. We have investigated the lifetimes and kinetics of cations derived from *sec*-alkanediazonium ions, generated photochemically from oxadiazoline precursors (**1**, eq 1),<sup>26,27</sup> using this probe method. We suggest that the 1,3,5-trimethoxybenzene probe methodology described below can also be applied to probe the kinetics of other electrophiles.

## Results

**1. Cyclohexadienyl Cations by LFP. (a) Protonation of Diazoalkanes.** Rate constants for proton transfer ( $k_{\text{HA}}$ ) from trifluoroacetic acid (TFA) to diazoalkanes **2a–d** (eq 1) in acetonitrile, trifluoroethanol (TFE), and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) were measured by monitoring the decays of the diazo bands in UV-LFP experiments, or in laser flash photolysis experiments utilizing time-resolved infrared detection (TRIR-LFP),<sup>28</sup> following 308 nm LFP of the corresponding oxadiazoline precursor (**1**, eq 1). In the presence of acids, these



absorptions decay with pseudo-first-order kinetics. Bimolecular rate constants for protonation were obtained as the slopes of linear plots of observed rate constants<sup>29</sup> vs acid concentration (Table 1).

Weakly nucleophilic polar solvents were chosen in order to maximize the lifetimes of the cationic intermediates generated upon protonation of diazoalkanes **2a–d**. Highly reactive cations such as benzyl cations<sup>30</sup> or the 9-fluorenyl cation<sup>31</sup> have been observed in LFP experiments in HFIP, suggesting that this

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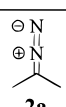
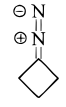
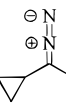
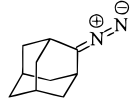
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**Table 1.** Rate Constants for Proton Transfer to Diazoalkanes ( $k_{\text{HA}}$ ) in acetonitrile, TFE, and HFIP at 22 °C<sup>a</sup>

Diazoalkane	Solvent	$k_{\text{HA}}, \text{M}^{-1} \text{s}^{-1}$ <sup>b</sup>
 <b>2a</b>	MeCN	$k_{\text{TFA}} = (6.8 \pm 0.4) \times 10^6$
	TFE	$k_{\text{TFA}} = (1.2 \pm 0.3) \times 10^7$
	HFIP	$k_{\text{TFA}} = (4.0 \pm 0.7) \times 10^7$
 <b>2b</b>	MeCN	$k_{\text{TFA}} = (4.3 \pm 0.1) \times 10^7$
	TFE	$k_{\text{TFA}} = (1.2 \pm 0.1) \times 10^8$
	HFIP	$k_{\text{TFA}} = (2.9 \pm 0.7) \times 10^8$
 <b>2c</b>	MeCN	$k_{\text{TFA}} = (4.8 \pm 0.3) \times 10^6$
	TFE	$k_{\text{TFA}} = (5.5 \pm 0.6) \times 10^6$
	HFIP	$k_{\text{TFA}} = (8.0 \pm 0.5) \times 10^6$
 <b>2d</b>	MeCN	$k_{\text{TFA}} = (1.4 \pm 0.1) \times 10^7$
	TFE	$k_{\text{TFA}} = (2.9 \pm 0.3) \times 10^7$
	HFIP	$k_{\text{TFA}} = (5.1 \pm 0.4) \times 10^7$

<sup>a</sup> Measured by UV-LFP at 250 nm. <sup>b</sup>  $k_{\text{TFE}}$  and  $k_{\text{HFIP}}$  were found to be less than  $10^4 \text{ s}^{-1}$  in all cases. <sup>c</sup> Measured by TRIR-LFP at 2037  $\text{cm}^{-1}$ .

solvent is sufficiently polar to allow ionic intermediates to exist and sufficiently inert to preclude fast nucleophilic attack.

**(b) 1,3,5-Trimethoxybenzene Probe Reactions.** Attempts to observe alkanediazonium ions directly after 308 nm LFP of oxadiazolines **1a–d** by TRIR or UV-visible detection at ambient temperatures, or at low temperatures ( $-90 \text{ }^\circ\text{C}$ ,  $\text{CD}_2\text{Cl}_2$ , TFA or  $\text{HBF}_4$ ) after steady-state photolysis of oxadiazolines **1a**, proved to be fruitless. Instead we sought trapping reactions which would be compatible with the solvent system and lead to a product with a UV-visible chromophore that would be easily detected by UV-LFP. It is well established that  $\pi$ -nucleophiles react readily with carbocations.<sup>32</sup> When arenes react with carbocations cyclohexadienyl cations are formed as intermediates. Cyclohexadienyl cations are relatively unreactive cationic intermediates<sup>33</sup> with UV absorptions ranging from 340 to 400 nm,<sup>33</sup> with high extinction coefficients<sup>33b</sup> ( $\epsilon \sim 10000$ ). The highly reactive fluorenyl cation ( $\text{FL}^+$ ) has been shown to react with mesitylene as well as other electron-rich aromatics via electrophilic aromatic addition, and rate constants for these reactions have been measured by LFP.<sup>34</sup> It is well known that oxygen-substituted cations are more stable than their analogous alkyl-substituted counterparts, and therefore the electron-rich 1,3,5-trimethoxybenzene (TMB) was chosen as the probe  $\pi$ -nucleophile.

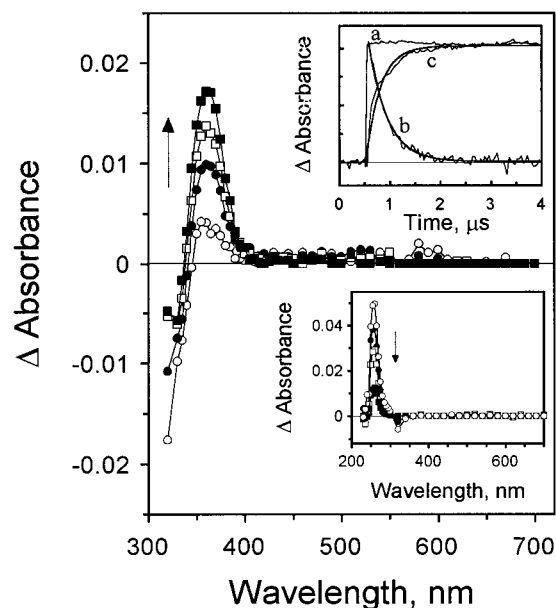
Kinetics of the reactions of  $\text{TMBH}^+$  with nucleophiles such as halide ions and alcohols have been studied previously by

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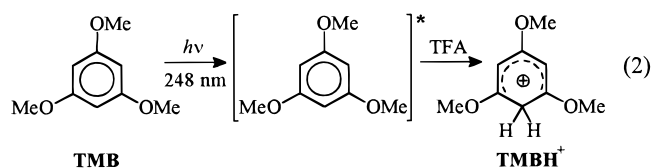
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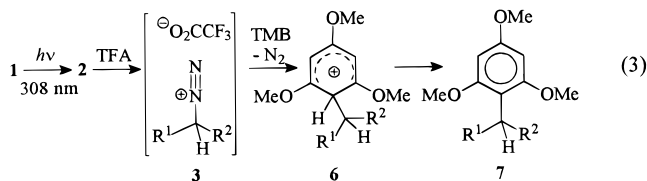
**Figure 1.** Time-resolved UV-vis spectra of 1-cyclobutyl-2,4,6-trimethoxybenzenium ion obtained after 308 nm LFP of **1b** in HFIP containing 1.34 M TMB and 0.002 M TFA at 22 °C. The data were collected at intervals of 260 ns (○), 620 ns (●), 720  $\mu\text{s}$  (□), and 2.3  $\mu\text{s}$  (■) after the laser pulse. Lower inset shows the time-resolved UV-visible spectra obtained after 308 nm LFP of **1b** in HFIP containing 0.002 M TFA at 22 °C with the data collected at the same time intervals. Upper inset shows the time-resolved UV-visible absorption traces (overlaid and normalized) observed at 250 nm (a, stable intermediate; b, decay) and 355 nm (c, growth) wavelengths following 308 nm LFP of (a) **1b** in HFIP, (b) in HFIP containing 0.002 M TFA, and (c) in HFIP containing both 1.34 M TMB and 0.002 M TFA.

excited state protonation of TMB (eq 2).<sup>33</sup> Low reactivity of  $\text{TMBH}^+$  toward nucleophiles was established ( $k_{\text{Nu}} \sim 10^2\text{--}10^3$  or smaller in HFIP) suggesting that closely related cations resulting from electrophilic aromatic addition reactions ( $\text{TM-BR}^+$ ) should be good probes for the study of more reactive cations ( $\text{R}^+$ ) since they can be quenched by added nucleophiles without appreciable quenching of the  $\text{TMBR}^+$ . LFP (308 nm)



of oxadiazolines **1a–d** in the presence of 1.34 M TMB and  $2.0 \times 10^{-3} \text{ M}$  TFA in HFIP led to persistent (stable on the timescales of the experiments) absorptions with  $\lambda_{\text{max}} \sim 350\text{--}380 \text{ nm}$ , assigned to the cyclohexadienyl cations **6a–d** (eq 3). The transient absorptions grew in with the same rate constants (within experimental error) as those for the decay of the diazo band observed at 250 nm by UV-LFP or at 2037  $\text{cm}^{-1}$  by TRIR-LFP (Figure 1). The growths and decays were not affected by the presence of molecular oxygen. Time-resolved UV-visible spectra acquired (300–700 nm) after 308 nm LFP, under identical conditions in the absence of oxadiazoline, did not show any signals associated with excited state protonation of TMB.

Absorptions with  $\lambda_{\text{max}} \sim 350\text{--}370 \text{ nm}$  for cyclohexadienyl cations **6a–d** were also observed after 308 nm LFP of solutions of oxadiazolines **1a–d**, in the presence of 1.34 M TMB and various concentrations of TFA in 2,2,2-trifluoroethanol (TFE) and in aqueous acetonitrile solvent. Again the UV-visible signals, assigned to cyclohexadienyl cations **6a–d**, appeared



with the same rate constants (within experimental error) as those for the disappearance of the corresponding diazoalkane. It was found that the absorbances associated with cyclohexadienyl cations **6a–d** were stable on the millisecond time scale in both solvents. These observations confirmed that the transients, assigned to **6a–d**, are derived from protonation of the corresponding diazoalkane and that proton transfer is the rate-determining step in the formation of cyclohexadienyl cations **6a–d**.

For comparison,  $\text{TMBH}^+$  was also generated by 266 nm LFP of TMB in aqueous acetonitrile and in TFE in the presence of 0.01–0.05 M TFA. We confirmed its low reactivity toward nucleophiles in both solvent systems and also found that the reactions of  $\text{TMBH}^+$  with  $\text{Cl}^-$  and with  $\text{Br}^-$  were too slow to measure by LFP which is consistent with the results reported by McClelland and Steenken.<sup>33</sup> Values of  $\lambda_{\text{max}}$  for  $\text{TMBH}^+$  in TFE and in aqueous acetonitrile containing TFA were found to be  $\sim 345$ – $350$  nm (broad absorption maxima). Broad absorptions between  $\sim 500$  and  $630$  nm ( $\lambda_{\text{max}} \sim 595$  nm) were also observed and assigned to the TMB radical cation ( $\text{TMBH}^{\bullet+}$ ). The absence of these absorptions in the electrophilic aromatic addition reactions described earlier suggests that they do not proceed via an electron transfer mechanism.

(c) **Stern–Volmer Quenching Experiments.** In all cases the cyclohexadienyl cations **6a–d** were formed with the same rate constants as those for the disappearance of the corresponding photochemically generated precursor diazoalkane (eq 4).

$$k_{\text{obs}} = k_0 + k_{\text{HA}}[\text{HA}] \quad (4)$$

However, the yields of cyclohexadienyl cations as a function of TMB concentration, which are proportional to the intensities of the UV-visible absorbances of these cations, are governed by the relative rate constants in the product-determining steps. The rate law for the reaction of the carbocations is in eq 5 and the rate constants leading to products are in eqs 6 and 7.

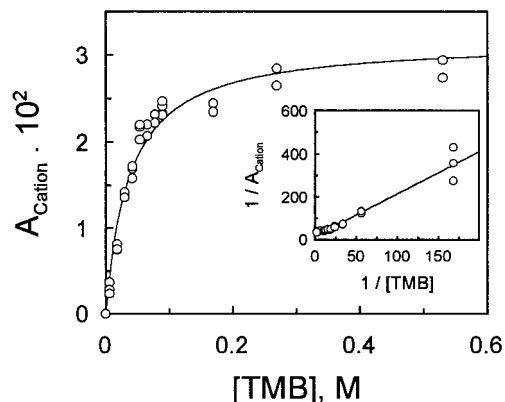
$$\frac{-d[\text{R}^1\text{R}^2\text{CH}^+]}{dt} = k_{\text{obs}}[\text{R}^1\text{R}^2\text{CH}^+] \quad (5)$$

$$k_{\text{obs}} = k_0 + k_{\text{TMB}}[\text{TMB}] \quad (6)$$

$$k_0 = k_{\text{coll}} + k_{\text{s}}[\text{solvent}] + \sum k_{\text{Nu}}[\text{nucleophile}] \quad (7)$$

Stern–Volmer type analyses<sup>35</sup> relate the yields of product of a trapping reaction as a function of trap concentration to that for the trapping reaction at infinite trap concentration. Such an analysis is based on the competition of all other reactions of an intermediate ( $k_0$ ) with the trapping reaction ( $k_{\text{TMB}}[\text{TMB}]$  in this case) and assumes that all of the intermediate is consumed in the trapping reaction at infinite trap concentration. The lifetimes of cations **4a–d** were determined by Stern–Volmer analysis of the maximum amplitudes of the cyclohexadienyl cation absorptions as a function of  $[\text{TMB}]$ . The data were analyzed by linear least squares fitting of the curve to eq 8, and by double

(35) Platz, M. S.; Modarelli, D. A.; Morgan, S.; White, W. R.; Mullins, M.; Celebi, S.; Toscano, J. P. *Progress in Reaction Kinetics*; Rodgers, M. A., Ed.; Elsevier: New York, 1994, 19, 93, and references therein.



**Figure 2.** Absorbance of 1-cyclobutyl-2,4,6-trimethoxybenzenium ion vs TMB concentration in HFIP at 22 °C. Inset shows the double reciprocal plot of  $1/\text{absorbance}$  of 1-cyclobutyl-2,4,6-trimethoxybenzenium ion vs  $1/\text{TMB}$  concentration in HFIP at 22 °C.

reciprocal treatment of the data (eq 9).<sup>35</sup> A typical plot is shown in Figure 2. In eqs 8 and 9,  $A_{\text{Cation}}$  is the amplitude of absorbance of the cyclohexadienyl cation in the presence of various amounts of added TMB,  $A_{\text{Cation}}^\infty$  is the amplitude of absorbance of the cyclohexadienyl cation at infinite  $[\text{TMB}]$  at a constant laser light intensity,  $k_0$  is the sum of all the rate constants leading to the disappearance of the transient cation in the absence of the quencher,  $\tau = 1/k_0$  is the lifetime of the transient cation, and  $k_{\text{TMB}}$  is the bimolecular rate constant for the reaction of the cation with TMB. Fitting the data to the curve in eq 9 allows one to solve for the product  $k_{\text{TMB}}\tau$  directly without using intercept:slope ratios (which are equal to  $k_{\text{TMB}}/k_0$ ) from double reciprocal plots (eq 9).

$$\frac{A_{\text{Cation}}}{A_{\text{Cation}}^\infty} = \frac{k_{\text{TMB}}[\text{TMB}]}{k_0 + k_{\text{TMB}}[\text{TMB}]} = \frac{k_{\text{TMB}}\tau[\text{TMB}]}{1 + k_{\text{TMB}}\tau[\text{TMB}]} \quad (8)$$

$$\frac{1}{A_{\text{Cation}}} = \frac{k_0}{A_{\text{Cation}}^\infty k_{\text{TMB}}[\text{TMB}]} + \frac{1}{A_{\text{Cation}}^\infty} \quad (9)$$

The lifetimes of cations **4a–d** determined in aqueous acetonitrile, TFE, and HFIP are summarized in Table 2.

(d) **Azide Clock.** In order to estimate the lifetimes of secondary carbocations derived from *sec*-alkanediazonium ions in solution, we first needed to determine the rate constants for reactions of the carbocations with TMB. The azide ion, which reacts with highly electrophilic carbocations at the diffusion-controlled rate<sup>36–38</sup> with  $k_{\text{N}_3^-} \approx 5 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ ,<sup>39</sup> was used to clock the electrophilic aromatic addition reactions. Bimolecular rate constants for the reactions of cations **4a–d** with nucleophilic traps were determined by keeping the TMB concentration constant and varying the concentration of nucleophile (e.g., azide ion, eq 10). Linear least-squares analysis of the ratio ( $A_{\text{Cation}}^\infty/A_{\text{Cation}}$ ) vs nucleophile concentration, with the y-intercept defined as 1, according to the Stern–Volmer<sup>35</sup> relation in eq 11, gives a slope which is equal to  $k_{\text{Nu}}/k_{\text{TMB}}[\text{TMB}]$ . In eq 11,  $A_{\text{Cation}}^\infty$  and  $A_{\text{Cation}}$  are the amplitudes of absorbance of the cyclohexadienyl cation in the absence and presence of added nucleophile, and  $k_{\text{Nu}}$  is the bimolecular rate constant for the reaction of the nucleophile with the cation.





(36) Richard, J. P.; Rothenberg, M. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, 106, 1361.

(37) Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, 106, 1373.

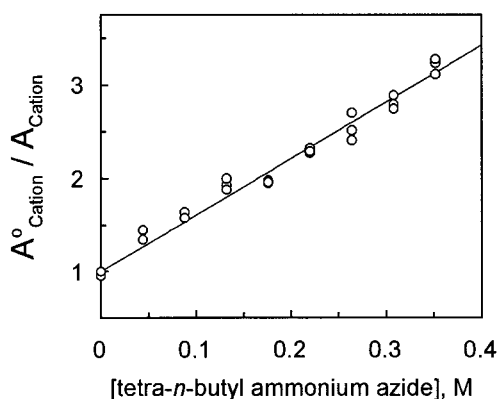
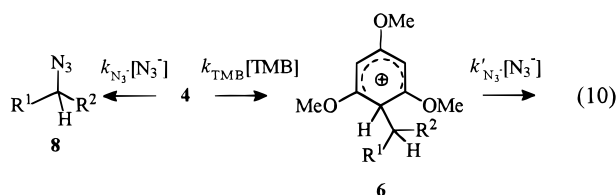
(38) Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1982**, 104, 4691.

(39) McClelland, R. A.; Kanagasabayath, V. M.; Banait, N. S.; Steenken, S. *J. Am. Chem. Soc.* **1991**, 113, 1009.

**Table 2.** Lifetimes of Carbenium Ions Deduced Using the Trimethoxybenzenium Ion Probe Technique

Cation	Solvent	$k_{\text{TMB}} \cdot \tau$ , M <sup>-1</sup> (Curve Fit)	$\tau$ , ns	$k_o$ , s <sup>-1</sup> <sup>a</sup>
 4a	MeCN (aq.)	0.25 ± 0.12	0.05	2.0 × 10 <sup>10</sup> <sup>b</sup>
	TFE	0.68 ± 0.14	0.14	7.4 × 10 <sup>9</sup> <sup>b</sup>
	HFIP	0.70 ± 0.22	0.14	7.1 × 10 <sup>9</sup> <sup>b</sup>
 4b	MeCN (aq.)	0.30 ± 0.04	0.06	1.7 × 10 <sup>10</sup> <sup>b</sup>
	TFE	2.3 ± 0.21	0.50	2.1 × 10 <sup>9</sup> <sup>c</sup>
	HFIP	27 ± 1.5	5.5	1.8 × 10 <sup>8</sup> <sup>c</sup>
 4c	MeCN (aq.)	0.89 ± 0.07	0.18	5.6 × 10 <sup>9</sup> <sup>b</sup>
	TFE	20 ± 0.21	4.1	2.5 × 10 <sup>8</sup> <sup>c</sup>
	HFIP	180 ± 27	37	2.7 × 10 <sup>7</sup> <sup>c</sup>
 4d	MeCN (aq.)	0.62 ± 0.09	0.12	8.1 × 10 <sup>9</sup> <sup>b</sup>
	TFE	1.6 ± 0.44	0.33	3.1 × 10 <sup>9</sup> <sup>b</sup>
	HFIP	1.7 ± 0.35	0.34	2.9 × 10 <sup>9</sup> <sup>b</sup>

<sup>a</sup> Assuming  $k_{\text{TMB}} = 5 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$  (see Table 3). <sup>b</sup>  $k_o = k_{\text{coll}} + k_s + k_s'$  (see Scheme 3 and Discussion),  $k_o$  values are lower limits for  $k_s$ . <sup>c</sup>  $k_o \sim k_s$ .

**Figure 3.** Stern–Volmer quenching plot for the reaction of cyclobutonium ion with azide ion in the presence of 0.16 M TMB in HFIP at 22 °C.

$$\frac{A^\circ_{\text{Cation}}}{A_{\text{Cation}}} = \frac{k_{\text{Nu}}}{k_{\text{TMB}}[\text{TMB}]}[\text{nucleophile}] + 1 \quad (11)$$

Such quenching plots were constructed for the reactions of cations **4a–d** with azide ion (Figure 3) and bromide ion, and the results are summarized in Table 3.

Cations **6a–d** decayed with pseudo-first-order kinetics in the presence of added azide ion, with much lower rate constants ( $k_{\text{N}_3^-} = 1\text{--}4 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ ) than those of cations **4a–d**. The formation of cations **6a–d** and their decay in the presence of added azide were resolvable in LFP experiments.

The rate constants of reactions of  $\text{Br}^-$  with cations **4a–d** were of the same order of magnitude as those for their reactions with  $\text{N}_3^-$ . On the other hand, cyclohexadienyl cations **6a–d**

**Table 3.** Rate Constants and Rate Constant Ratios in TFE at 22 °C

cation	nucleophile			
	$\text{N}_3^-$		$\text{Br}^-$	
	$k_{\text{TMB}}/k_{\text{N}_3^-}$	$k_{\text{TMB}}$ , M <sup>-1</sup> s <sup>-1</sup>	$k_{\text{TMB}}/k_{\text{Br}^-}$	$k_{\text{Br}^-}$ , M <sup>-1</sup> s <sup>-1</sup>
<b>4a</b>	0.89 <sup>a</sup>	4.5 × 10 <sup>9</sup> <sup>b,d</sup>	1.0	5 × 10 <sup>9</sup>
<b>4b</b>	0.94 <sup>a</sup>	4.7 × 10 <sup>9</sup> <sup>b</sup>	1.0	5 × 10 <sup>9</sup>
<b>4c</b>	0.92 <sup>a</sup>	4.6 × 10 <sup>9</sup> <sup>b</sup>	1.0	5 × 10 <sup>9</sup>
<b>4d</b>	0.93 <sup>a</sup>	4.6 × 10 <sup>9</sup> <sup>b,d</sup>	1.0	5 × 10 <sup>9</sup>
<b>6a</b>	—	3.8 × 10 <sup>6</sup>	—	<i>c</i>
<b>6b</b>	—	4.0 × 10 <sup>6</sup>	—	<i>c</i>
<b>6c</b>	—	2.5 × 10 <sup>6</sup>	—	<i>c</i>
<b>6d</b>	—	3.7 × 10 <sup>6</sup>	—	<i>c</i>

<sup>a</sup> May be an underestimation as a result of azide/hydrazoic acid equilibrium in solutions of 0.002 M TFA in TFE. <sup>b</sup> Assuming  $k_{\text{N}_3^-} = 5 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ .<sup>39</sup> <sup>c</sup> Too small to measure. <sup>d</sup> Lower limits due to preassociation reactions within the first solvent shell.

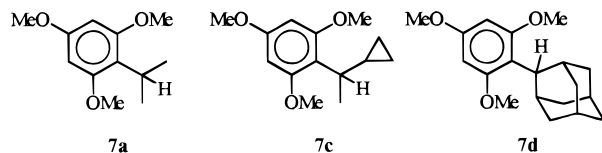
**Table 4.** Yields of Products from Steady-State Photolysis Experiments<sup>a,b</sup>

cation	solvent	% TMB adduct	% solvent adduct	% elimination product	$k_{\text{TMB}}/k_s$ , M <sup>-1</sup>
<b>4a</b>	HFIP	6.9	90	<1	3.9 × 10 <sup>-2</sup>
	TFE	8.6	92	<1	4.7 × 10 <sup>-2</sup>
	benzene <sup>d,e</sup>	8.0	—	—	—
<b>4b</b>	HFIP	>95	<i>c</i>	<1	—
	HFIP <sup>f</sup>	21	<i>c</i>	<1	30
	TFE	80	16	<1	2.5
<b>4c</b>	benzene <sup>d</sup>	>50	<i>c</i>	<1	—
	HFIP	>95	<i>c</i>	<1	280
	HFIP <sup>f</sup>	74	26	<1	—
<b>4d</b>	TFE	>95	<i>c</i>	<1	—
	benzene <sup>d</sup>	>90	<i>c</i>	<1	—
	HFIP	7.4	90	<1	4.1 × 10 <sup>-2</sup>
	TFE	14.5	82	<1	8.9 × 10 <sup>-2</sup>
	benzene <sup>d,e</sup>	15.5	<i>c</i>	3/8	—

<sup>a</sup> Minor side products from the photolysis of oxadiazolines were detected in some cases. <sup>b</sup> Solutions were 2.0 M in TMB. <sup>c</sup> Not detected in the GC/GC-MS experiments. <sup>d</sup> Solutions were 4.5 M in TMB with TFA as the proton source. <sup>e</sup> Ion pair collapse product is the dominant product of reaction and makes up the remainder of the material. <sup>f</sup> Solutions were 0.1 M in TMB.

did not react with  $\text{Br}^-$  at an appreciable rate. The low reactivity of 1-alkyl-2,4,6-trimethoxybenzenium ions toward nucleophiles, exemplified by the slow reactions of **6a–d** with  $\text{N}_3^-$  and  $\text{Br}^-$ , makes electrophilic addition reactions to TMB a versatile kinetic probe reaction.

**2. Steady-state Photolysis Experiments. (a) Electrophilic Aromatic Addition/Substitution.** Solutions of 2.0 M TMB in HFIP, in TFE, and in benzene containing 0.01 M of oxadiazoline **1a**, **1b**, **1c**, or **1d** were placed in Pyrex reaction vessels (1 mL each) fitted with septa, degassed with  $\text{N}_2$ , and irradiated for 2 h in a Rayonet reactor fitted with 6–12 300 nm bulbs. HFIP and TFE were both acidic enough to protonate the resulting diazoalkanes **2a–d**, whereas 0.01 M TFA was added to the benzene solutions after photolysis. The resulting solutions were analyzed by GC-MS and, in some cases, by <sup>1</sup>H-NMR. Yields are reported in Table 4. In each case, products of electrophilic aromatic substitution (**7a–d**) were observed in addition to solvent-derived products, elimination products, and ion pair collapse products.



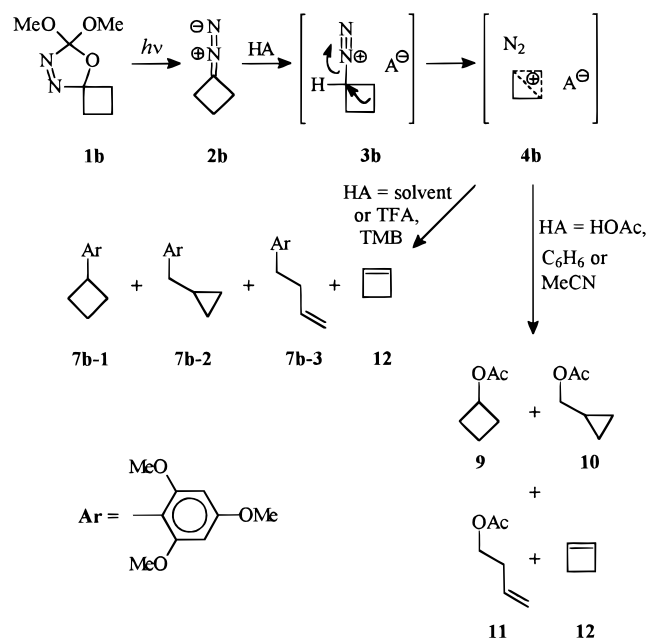
**Table 5.** Product Distributions from Protonation of Diazocyclobutane

solvent	7b-1:7b-2:7b-3 <sup>a</sup>	% cyclobutene
HFIP	21.3:7.1:0	trace, <0.1
TFE	25.0:9.7:1.0	trace, <0.1
benzene	2.3:1.0 <sup>b</sup>	trace, <0.1

solvent	9:10:11 <sup>c</sup>	% cyclobutene
benzene	6.3:6.9:1.0	trace, <0.1
acetonitrile	3.9:5.1:1.0	trace, <0.1

<sup>a</sup> Solutions were 2.0 M in TMB. <sup>b</sup> 7b-3 not detected. <sup>c</sup> Solutions were 0.1 M in HOAc.

**Scheme 2**

Products from ion pair collapse or from reactions with solvent were not detected from precursors **1b** and **1c** in HFIP solvent (protonating acid = solvent or TFA) for solutions of 2.0 M TMB. For the reactions involving protonation of diazocyclobutane in the presence of TMB, three electrophilic aromatic substitution products, **7b-1**, **7b-2**, and **7b-3** (Scheme 2), were observed in HFIP, TFE, and benzene solvents. The ratios of products are listed in Table 5.

Steady-state photolyses of oxadiazoline **1b** in benzene or acetonitrile containing 0.1 M acetic acid gave products **9–12** (Scheme 2). These observations are consistent with decomposition via the bicyclobutonium ion intermediate **4b**. The unimolecular dissociation of cyclobutyl diazonium ion (**3b**) may proceed with “anchimeric assistance” from the adjacent carbon atom in the transition-state for N<sub>2</sub> loss (Scheme 2). The observed product ratios are all in close agreement with those observed for the deamination of cyclobutyl amine.<sup>40</sup>

**(b) Elimination vs Electrophilic Addition.** Only trace amounts of elimination products<sup>41,42</sup> propene, cyclobutene,

(40) Mazur, R.H.; White, W.N.; Semenow, D.A.; Lee, C.-C.; Silver, M.S.; Roberts, J.D. *J. Am. Chem. Soc.* **1959**, *81*, 4390.

(41) Factors which govern competitive solvolytic elimination mechanisms have been actively studied recently, and it has been shown that high acidity of the  $\beta$ -hydrogen is required for E2 elimination to compete. See: (a) Pirinccioglu, N.; Thibblin, A. *J. Am. Chem. Soc.* **1998**, *120*, 6513, and references therein. It is possible that elimination occurs via an E2 mechanism within the diazonium ion counterion pairs; however, it would be difficult to distinguish between the mechanistic possibilities because the transition state for the E2 reaction would most likely resemble that of the E1 reaction due to the leaving group ability of N<sub>2</sub>.

cyclopropylethylene, and dehydroadamantane were detected from photolyses of oxadiazolines **1a**, **1b**, **1c**, and **1d**, respectively in HFIP, TFE, or benzene. The lack of elimination products from **4b** and **4c** is presumably the result of ring strain in the products. The 2-adamantyl cation apparently shows little propensity for 1,2-shifts and 1,2-elimination is not favored due to ring strain in the bridgehead alkene product; however, 1,3-elimination can occur.<sup>43</sup>

**Discussion**

**1. TMB Probe Reactions.** Utilizing oxadiazolines **1** as photochemical precursors to diazo compounds, we determined the lifetimes of “invisible” simple secondary carbocations in HFIP, TFE, and MeCN with the aid of TMB as a kinetic probe. Carbocations **4a–d** react with TMB by electrophilic aromatic addition with rate constants ( $\sim 5 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ ) that approach the diffusion-controlled limit as determined by azide clocking experiments. These rate constants are consistent with those for reactions of other reactive carbocations, such as fluorenyl cation,<sup>44</sup> with arenes. Electrophilic aromatic additions of **4a–d** onto TMB give rise to cyclohexadienyl cations **6a–d** ( $\sigma$ -complexes) which possess absorbances that are detectable (“visible”) by UV-LFP. The cyclohexadienyl cations are ultimately deprotonated by Brønsted bases (solvent) giving rise to substituted arene products, as determined by product studies. In HFIP, TFE, and MeCN, cations **6a–d** are stable on the timescales of the UV-LFP experiments. They react very sluggishly with nucleophiles such as solvent (too slow to measure by LFP) and are rather unreactive even with azide ions ( $k_{\text{N}_3^-} \sim 1 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ ). Cations **4a–d** undergo reactions with nucleophiles with rate constants that are at least 3 orders of magnitude larger than those of **6a–d**. The remarkably different reactivities of carbocations **4a–d** and those of cations **6a–d** toward nucleophiles make these reactions versatile kinetic probes.

**2. Rate-Limiting Proton Transfer.** In the sequence of reactions following oxadiazoline photolysis leading to the formation of cyclohexadienyl cations **6a–d**, the rate-determining step was always proton transfer to diazoalkanes **2a–d**. This is in keeping with rapid irreversible loss of N<sub>2</sub> from the *sec*-alkanediazonium ions compared with back proton transfer. The product-determining steps are reactions of **4a–d**, and it is those steps which the Stern–Volmer quenching experiments with TMB probe. In contrast, protonations of diazomethane and primary-diazoalkanes are generally reversible, and attack by nucleophiles is rate limiting.<sup>8–11</sup>

**3. Lifetimes of Cations and Kinetic Stabilities.** The lifetimes reported in Table 2 are most likely those of dialkyl carbocations within ion pair **4**, or from diffusionally equilibrated “free” dialkyl carbocations according to Scheme 3.

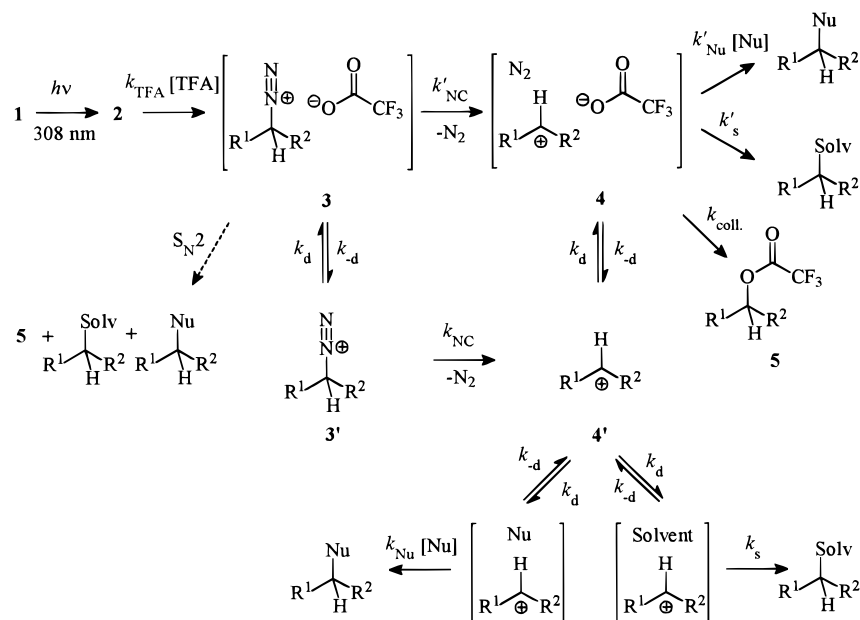
Reactions involving concerted attack by solvent or other nucleophiles onto alkanediazonium ions **3a–d** (S<sub>N</sub>2) are inconsistent with product studies performed from **1b** and inconsistent with a mass of previously reported literature implicating *sec*-carbocations from *sec*-alkanediazonium ions.<sup>8–11</sup> Rate constants for nucleophilic attack (S<sub>N</sub>2) by water and hydroxide ion

(42) Concerted eliminations may occur in solvolysis reactions; however, they are unlikely with N<sub>2</sub> as a neutral leaving group: Toteva, M. M.; J. P. Richard *J. Am. Chem. Soc.* **1996**, *118*, 11434.

(43) For analogous reactions, see: (a) Gassman, P. G.; Talley, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 1214. (b) Gassman, P. G.; Talley, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 4138. (c) Gassman, P. G.; Saito, K.; Talley, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 7613.

(44) Cozens, F.; Li, J.; McClelland, R. A.; Steenken, S. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 743.

## Scheme 3



on methanediazonium ion have been estimated to be  $1.8 \text{ s}^{-1}$  and  $1 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ , respectively.<sup>11</sup> The magnitudes of these rate constants imply that there is a significant barrier to nucleophilic substitution of molecular nitrogen ( $S_N2$ ) and barriers for *sec*-alkanediazonium ions would undoubtedly be larger still.

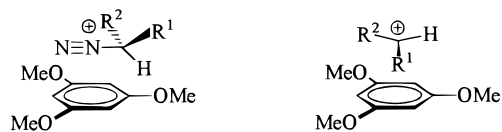
For carbocations **4a** and **4d** it is likely that a significant proportion are captured from within their respective ion pairs, even with trifluoroacetate as the counterion, because of high yields of products from ion pair collapse.<sup>45</sup> Simple dialkyl cations stabilized only by inductive effects are expected to have little or no chemical barrier to cation–nucleophile combination reactions.<sup>46</sup> There are no significant solvent effects on the lifetimes of **4a** and **4d** in HFIP, TFE, and MeCN (aq). This suggests that the rate constants for addition of these solvents are not activation limited, but rather are limited by a process such as reorganization of the solvation shell that places a solvent molecule in a reactive configuration. If this is the case, then the observed rate constants for addition of solvent by rate-determining solvent reorganization can only set a lower limit on the rate constant for nucleophilic addition of solvent to **4a** and **4d** which occurs after this reorganization. It is possible that the rate constants for reactions with solvent ( $k_o$ ) for cations **4a** and **4d** in Table 2 represent a composite of those from ion pairs and those from diffusively equilibrated cations. Since ion pair collapse would also be limited by solvation shell reorganization, the rate constants for diffusional separation of ion pairs must be upper limits for the lifetimes of the alkanediazonium ion precursors. If the alkanediazonium ions are longer lived then they would diffuse away from the trifluoroacetate counterion and cations **4a** and **4d** would be born with only solvent in their first solvation shells. In such cases the yields of products of ion pair collapse would be negligible. A consequence of reactions of **4a** and **4d** within ion pairs is that cation–nucleophile combination reactions with other nucleophiles probably occur, at least in part, by a preassociation mechanism.<sup>47</sup>

(45) Yields were variable and were as high as 90% depending on the solvent and [TMB]. Exact yields were not determined. Products containing trifluoroacetate groups were unstable to GC conditions and different yields were obtained with various column conditions.

(46) Richard, J. P. *Tetrahedron* **1995**, *51*, 1535.

(47) Jencks, W. P. *Chem. Soc. Rev.* **1981**, *10*, 345.

Further evidence that reactions of cations **4a** and **4d** with solvent have little or no activation barriers comes from discrepancies between the ratios of rate constants ( $k_{TMB}/k_o$ ) measured by LFP and analogous ratios determined by product studies for precursors **1a** and **1d** (assuming  $k_o \sim k_s$ , Table 4). Smaller ratios were determined by product studies when HFIP or TFE were the protonating acid. Capture by solvent in the latter reactions gives the same products as ion pair collapse resulting in an increase in the apparent  $k_s$ . The discrepancy may also reflect medium effects on going to 2.0–4.5 M TMB. Lower solvent polarity would presumably lead to shorter lifetimes for the cationic species. Also, a redistribution of products within a cation–arene  $\pi$ -complex may occur. It has been suggested that transition states for aromatic substitution involving highly reactive electrophiles resemble  $\pi$ -complexes.<sup>48</sup> Cation– $\pi$  interactions can be considerable.<sup>49</sup> It is possible that, prior to electrophilic attack and  $\sigma$ -bond formation, either alkanediazonium ions **3a–d** and/or carbenium ions **4a–d** may form  $\pi$ -complexes with TMB and, from these complexes, partition between electrophilic addition and reaction with solvent and counterion. Large rate constants for some of the reactions with solvent would require preassociation of TMB with the diazonium ion precursors (either oxadiazoline or diazoalkane) through a  $\pi$ -complex which then yields cation  $\pi$ -complexes directly. Cation  $\pi$ -complexes could also lead to extended lifetimes in solution and explain differences in product distributions in the presence and absence of arene. There is precedence for such behavior in carbene chemistry.<sup>50</sup>

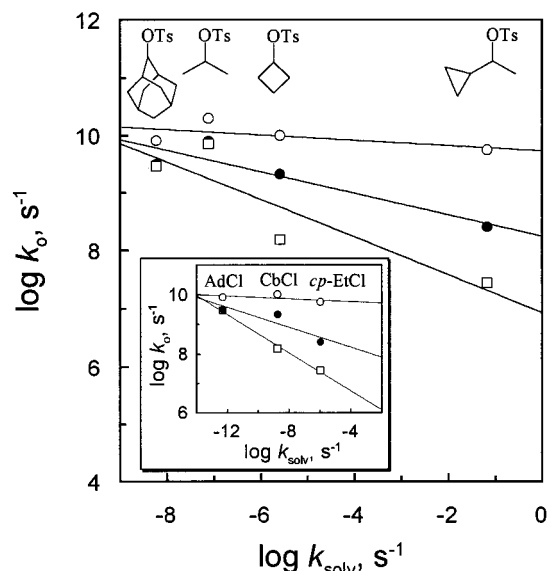


Products from ion pair collapse were not detected from precursors **1b** and **1c** in HFIP, or in TFE (protonating acid = solvent or TFA) for solutions of 2.0 M TMB. This suggests

(48) Olah, G. A. *Acc. Chem. Res.* **1971**, *4*, 420.

(49) Ma, J. C.; Dougherty, D. A. *Chem. Rev.* **1997**, *97*, 1303.

(50) Moss, R. A.; Yan, S.; Krogh-Jespersen, K. *J. Am. Chem. Soc.* **1998**, *120*, 1088.



**Figure 4.** Plots of  $\log k_0$  determined by the TMB kinetic probe method vs  $\log k_{\text{solv}}$  for the acetolyses of the analogous alkyl tosylates at 25 °C. The open circles, filled circles, and open squares represent the  $\log k_0$  data in 10% aqueous MeCN, TFE, and HFIP, respectively. The solid lines represent the linear least-squares fits of each set of data. Inset shows the plots of  $\log k_0$  determined by the TMB kinetic probe method vs  $\log k_{\text{solv}}$  for the solvolyses of the analogous alkyl chlorides in 80% aqueous acetone at 25 °C (see text).

that there are significant barriers to cation–nucleophile combinations for these cations and that they are diffusively equilibrated in these solvents.

**(a) Leaving Group Ability of  $\text{N}_2$ .** The solvolysis reactions of alkanediazonium ions, proceeding through carbocationic intermediates, represent the extreme in terms of leaving group ability. To illustrate this point we can compare the rate of dissociation of 2-adamantyl tosylate ( $k_{\text{solv}} \sim 4 \times 10^{-10} \text{ s}^{-1}$ , 25 °C in ethanol) with that of the dissociation of 2-adamantyl diazonium ion ( $k_{\text{solv}} \geq 3 \times 10^9 \text{ s}^{-1}$ , 22 °C in TFE); the ratio of rate constants is  $\sim 10^{19}$ !

The lifetimes measured from precursors **1a–d** are consistent with the relative stabilities of the dialkylcarbocations as measured by solvolysis rate constants for the corresponding alkyl tosylates<sup>51</sup> or alkyl halides.<sup>52</sup> Figure 4 shows linear free energy relationships between the  $\log k_0$  determined from precursors **1a–d** and the logarithms of solvolysis rate constants of analogous alkyl tosylates and alkyl chlorides.

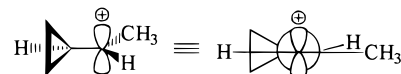
The solvolysis rate constants for 2-propyl tosylates in Figure 4 are larger than expected because of solvent assistance in the rate-limiting step,<sup>51i–k</sup> which probably does not occur for 2-propanediazonium ion. The observed rate constants  $k_0$  correlate roughly with analogous solvolysis rate constants, with a negative slope. The carbocation lifetimes ( $1/k_0$ ) should be roughly inversely proportional to the rate constants for solvolysis,

(51) (a) Roberts, D. D. *J. Org. Chem.* **1984**, *49*, 2521. (b) Bentley, T. W.; Bowen, C. T.; Brown, H. C.; Chloupek, F. J. *J. Org. Chem.* **1981**, *46*, 38. (c) Peters, E. N. *J. Am. Chem. Soc.* **1976**, *98*, 5627. (d) Roberts, D. D. *J. Org. Chem.* **1971**, *37*, 1510. (e) Bentley, T. W.; Jurczyk, S.; Roberts, K. *J. Chem. Soc., Perkin Trans. 2* **1987**, 293. (f) Gassman, P. G.; Saito, K. *Tetrahedron Lett.* **1981**, 1311. (g) Ando, T.; Tsukamoto, S. *Tetrahedron Lett.* **1977**, 2775. (h) Creary, X.; Geiger, C. C. *J. Am. Chem. Soc.* **1982**, *104*, 4151. (i) Fry, J. L.; Lancelot, C. J.; Lam, L. K. M.; Harris, J. M.; Bingham, R. C.; Raber, D. J.; Hall, R. E.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1970**, *92*, 2538. (j) Fry, J. L.; Harris, J. M.; Bingham, R. C.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1970**, *92*, 2540. (k) Schleyer, P. v. R.; Fry, J. L.; Lam, L. K. M.; Lancelot, C. J. *J. Am. Chem. Soc.* **1970**, *92*, 2542.

(52) Raber, D. J.; Harris, J. M.; Hall, R. E.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1971**, *93*, 4821, and references therein.

sis, giving rise to negative slopes in log–log correlations such as those in Figure 4.

**(b) Cyclobutonium Ion and 1-Cyclopropylethyl Carbocation.** The cyclobutyl cation is thought to exist as the nonclassical bicyclobutonium ion which is postulated to be in rapid equilibrium with the bisected cyclopropylcarbinyl cation.<sup>53</sup> The most energetically favorable conformer of ( $\alpha$ -methylcyclopropyl)carbinyl cation is the *trans* bisected structure below.<sup>53,54</sup>



Although there is much controversy regarding the relative stabilities of cyclopropyl- and phenyl-substituted carbocations, cyclopropylcarbinyl cations are thought to be at least as stable as the analogous phenyl-substituted carbocations thermodynamically, based on gas phase data<sup>55</sup> and  $pK_{\text{R}^+}$  values.<sup>56</sup> Chemical shift data for cyclopropyl- and phenyl-substituted carbocations, however, suggest that phenyl is slightly better at stabilizing positive charge.<sup>57</sup> Recently, the kinetic stabilities of substituted arylcyclopropylcarbenium ions have been investigated by LFP.<sup>58</sup> Kirmse and co-workers showed that cyclopropyl and phenyl groups are very similar in their ability to stabilize carbocations; however, the cyclopropyl group was found to be more sensitive to electron demand according to the slopes of Hammett plots for the reactions of the cations with TFE (for diarylcarbenium ions  $\rho^+ = 2.64$ , whereas for arylcyclopropylcarbenium ions  $\rho^+ = 4.34$ ). A more straightforward comparison of the relative kinetic stabilities of phenyl vs cyclopropyl-substituted carbocations involves direct comparison of the rate constants for reaction of the parent carbocations.

Although the lifetime of the benzyl carbocation ion in HFIP is not known, McClelland and co-workers predict that it should be 2–20 ns,<sup>30</sup> and the lifetime measured for the cyclobutonium ion using the TMB probe method is certainly of similar magnitude. Direct comparison of the lifetime of 1-cyclopropylethyl cation with that of 1-phenylethyl cation<sup>30</sup> in HFIP suggests that the latter is slightly more stable kinetically. This result, when compared with those of Kirmse and co-workers,<sup>58</sup> may

(53) (a) Olah, G. A.; Reddy, V. P.; Prakash, G. K. S. *Chem. Rev.* **1992**, *92*, 69. (b) Richey, H. G., Jr. In *Carbocation ions*; Olah, G. A., Schleyer, P. v. R., Eds.; Wiley-Interscience: New York, 1972; Vol. III, p 1201. (c) Wiberg, K. B.; Hess, A., Jr.; Ashe, A. J., III In *Carbocation ions*; Olah, G. A.; Schleyer, P. v. R., Eds.; Wiley-Interscience: New York, 1972; Vol. III, p 1295.

(54) Cyclopropyl groups adjacent to carbocations have been shown by X-ray crystallography to adopt bisecting conformations in several analogues. See: (a) Childs, R. F.; Kostyk, M. D.; Lock, C. J. L.; Mahendran, M. *J. Am. Chem. Soc.* **1990**, *112*, 8912. (b) Childs, R. F.; Faggiani, R.; Lock, C. J. L.; Mahendran, M. *J. Am. Chem. Soc.* **1986**, *108*, 3613. (c) Chadda, S. K.; Childs, R. F.; Faggiani, R.; Lock, C. J. L. *J. Am. Chem. Soc.* **1986**, *108*, 1694. (d) Childs, R. F.; Faggiani, R.; Lock, C. J. L.; Mahendran, M.; Zweep, S. D. *J. Am. Chem. Soc.* **1986**, *108*, 1692. (e) Childs, R. F.; Faggiani, R.; Lock, C. J. L.; Varadarajan, A. *Acta Crystallogr.* **1984**, *C40*, 1291. (f) Childs, R. F.; Varadarajan, A.; Lock, C. J. L.; Faggiani, R.; Fyfe, C. A.; Wasylshen, R. E. *J. Am. Chem. Soc.* **1982**, *104*, 2452.

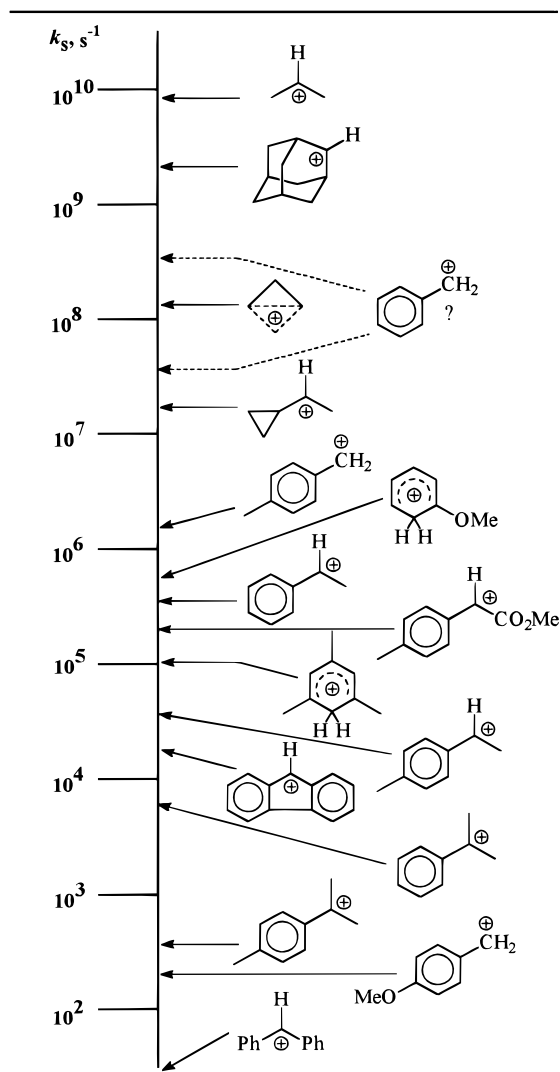
(55) (a) Wolf, J. F.; Harch, P. G.; Taft, R. W.; Hehre, W. J. *J. Am. Chem. Soc.* **1975**, *97*, 2902. (b) Taft, R. W.; Martin, R. H.; Lampe, J. *J. Am. Chem. Soc.* **1965**, *87*, 2490. (c) Deno, N. C.; Richey, H. G., Jr.; Liu, J. S.; Lincoln, D. N.; Turner, J. D. *J. Am. Chem. Soc.* **1965**, *87*, 4533.

(56) (a) Moss, R. A.; Shen, S.; Jespersen, K. K.; Potenza, J. A.; Schugar, H.-J.; Munjal, R. C. *J. Am. Chem. Soc.* **1986**, *108*, 134. (b) Kerber, R. C.; Hsu, C.-M. *J. Am. Chem. Soc.* **1973**, *95*, 3239.

(57) For example, the carbon bearing the positive charge in *c-prC*<sup>+</sup>(CH<sub>3</sub>)<sub>2</sub> has a chemical shift of  $\delta$  279.9 ppm, whereas that for PhC<sup>+</sup>(CH<sub>3</sub>)<sub>2</sub> is  $\delta$  254.2. See: (a) Olah, G. A.; Prakash, G. K. S.; Liang, G. *J. Org. Chem.* **1977**, *42*, 2666. (b) Olah, G. A.; White, A. M. *J. Am. Chem. Soc.* **1969**, *91*, 5801.

(58) Kirmse, W.; Krzossa, B.; Steenken, S. *J. Am. Chem. Soc.* **1996**, *118*, 7473.





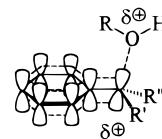
**Figure 5.** Reactivities of some carbocations toward HFIP at  $\sim 20^\circ\text{C}$ . Rate constants are from this work and from refs 22, 30, 31, 33, 58.

reflect differences in steric,<sup>59</sup> electronic, and solvation effects between the various substrates and is in keeping with the notion that phenyl and cyclopropyl groups have similar cation-stabilizing abilities. Figure 5 summarizes the relative reactivities of some carbocations in nonaqueous media<sup>22,30,31,33,58</sup> including those measured here. The TMB probe method has allowed us to define the upper region of Figure 5 for cations that are both “invisible” and too reactive to be measured directly by ns UV-LFP.

**(c) Barriers for Carbocation–Nucleophile Combination Reactions.** The simplest carbocation, methyl cation, is thought to undergo reactions with nucleophiles from within an encounter complex directly without passing over a barrier or through a transition state.<sup>46</sup> In the sequence from  $\text{CH}_3^+$  to product, the encounter complex is thought to be the transition state for the reaction. Barriers for carbocation–nucleophile combination reactions appear when substituents, particularly  $\pi$ -donating ones,

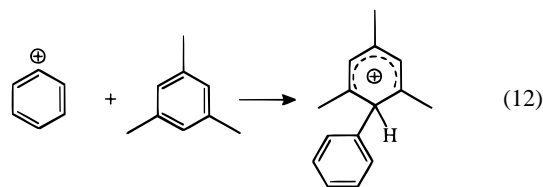
(59) It is unclear whether the twist angles of aryl groups in diaryl and arylcyclopropyl cations vary with substituent and whether such structural changes affect the reactivity of these species. Calculations regarding  $\text{Ph}_2\text{C}^+\text{H}$  show that the minimum energy structure has  $C_2$  symmetry and that both phenyls are rotated  $18.59^\circ$  out of the plane which is defined by the  $\text{sp}^2$ -hybridized carbocation carbon and the atoms directly attached to it (Amyes, T. L.; Richard, J. P.; Novak, M. *J. Am. Chem. Soc.* **1992**, *114*, 8032.), whereas the phenyl group in arylcyclopropylcarbenium ions can be out of plane by as much as  $27^\circ$ .<sup>55d</sup>

are added to the parent methyl cation.<sup>46</sup> Factors which affect the relative size of barriers to carbocation–nucleophile combination reactions are many and have been elaborately discussed in a comprehensive review by Richard.<sup>46</sup> Differences in reaction barriers for carbocation–nucleophile combination reactions of purely inductively stabilized carbocations result from changes in the thermodynamic driving force for the reactions. Less energetically favorable reactions have higher barriers to reaction as predicted by curve crossing of potential energy surfaces of constant curvature. Reaction barriers for resonance-stabilized carbocations, such as benzyl cations, are also affected by the thermodynamic changes, however, additional contributions to the barriers arise from increased Marcus intrinsic barriers<sup>60</sup> for reaction resulting mainly from the breaking of partial  $\pi$ -bonds to the carbocationic carbon atom at the transition state.<sup>46</sup>



The lifetimes of 2-propyl cation (**4a**) and 2-adamantyl cation (**4d**) are consistent with carbocation–solvent combination reactions that are highly exoergic and proceed with little or no chemical barriers to reaction even in weakly nucleophilic HFIP. The lack of selectivity of **4a,d** toward solvent, TMB, azide ion, and bromide ion appears to be the result of a Hammond effect. That is, the reactions all have very early transition states, and the barriers for these reactions are all similar. The barriers for carbocation–solvent combination reactions are much smaller than those for  $\pi$ -stabilized carbocations such as substituted benzyl cations.<sup>30</sup>

Interestingly, Steenken, McClelland, and co-workers have reported that the phenyl carbocation is relatively long lived in HFIP and reacts with mesitylene (eq 12) selectively over HFIP with  $k_{\text{Ar}}/k_{\text{HFIP}} \sim 10\text{ M}^{-1}$ .<sup>61,62</sup> Assuming that  $k_{\text{Ar}} \sim 5 \times 10^9\text{ M}^{-1}\text{ s}^{-1}$  then  $k_{\text{HFIP}} \sim 5 \times 10^8\text{ s}^{-1}$ . These findings seem surprising



considering that the phenyl cation is much less thermodynamically stable than any of the secondary carbocations studied here.<sup>63</sup> A kinetic factor unique to phenyl cations must exist that leads to increased barriers to carbocation–nucleophile combination reactions. One possibility is that the positive charge in phenyl cations is in fact delocalized through an open shell singlet resonance contributor with an electron in the formerly vacant orbital of the carbocation carbon and radical cation character in the aromatic fragment.<sup>64</sup> Such delocalization might lead to increased intrinsic barriers for reactions of phenyl cations with HFIP solvent. Polarization of the  $\pi$ -system in phenyl cations

(60) Marcus, R. A. *J. Phys. Chem.* **1968**, *72*, 891.

(61) Steenken, S.; Ashokkumar, M.; Maruthamuthu, P.; McClelland, R. A. *J. Am. Chem. Soc.* **1998**, *120*, 11925.

(62) Authors reported a dimensionless ratio of  $k_{\text{Ar}}/k_{\text{HFIP}} = 140$ .

(63) Phenyl diazonium ions are stable and isolable species in solution whereas *sec*-alkanediazonium ions, such as 2-propanediazonium ion, decompose spontaneously and have never been observed directly. See ref 10f.

(64) Personal communication from R. A. McClelland.

may also result in unfavorable electrostatic interactions in transition states for carbocation–nucleophile combination reactions.<sup>65</sup>

The lifetimes of cyclobutyl cation (**4b**) and of cyclopropylethyl cation (**4c**) are consistent with the increased thermodynamic stabilities of these carbocations relative to **4a,d**. Delocalization of positive charge through  $\pi$ -interactions of the Walsh orbitals of the cyclopropane ring in bisected structures or through nonclassical bonding, which is perturbed as cation–nucleophile bond formation occurs and as the former carbocation carbon undergoes rehybridization, probably leads to increased intrinsic barriers and contributes to the barrier heights for carbocation–solvent combination reactions.

It is concluded, on the basis of their magnitudes, that the lifetimes observed are those of cations **4a–d** which are at least partially, and in some cases completely, diffusionally separated from the trifluoroacetate counterion.<sup>66</sup> There also appears to be a solvent effect on the lifetimes of cations **4b,c**, in accord with the relative nucleophilicities of the different solvent systems, consistent with previous observations.<sup>22</sup> In an aqueous environment, cations **4a–d** most probably react within the first solvation shell.<sup>8,9b,22,46</sup>

**4. Biological Significance.** *N*-Methyl-*N*-nitroso-urea, *N*-methyl-*N*-nitro-nitrosoguanidine, *N*-nitroso(1-acetoxyethyl)methylamine, and diazomethane all show identical methylation patterns with a sequence-characterized DNA restriction fragment.<sup>67</sup> It has been shown that methylation by *N*-nitroso compounds occurs selectively at N<sup>7</sup> of guanine<sup>68</sup> with sequence selectivity attributed to the sequence dependent changes in nucleophilicity.<sup>68</sup> This is in contrast to patterns of ethylation which occurs at both oxygen and nitrogen. The O-alkylation of guanine is apparently more harmful than N-alkylation.<sup>69</sup> It has been postulated that secondary and benzyl derivatives alkylate DNA via carbocationic intermediates,<sup>10</sup> rather than diazonium ions, and that observed selectivities may be the result of preferential solvation of alkanediazoates prior to decomposition.<sup>8,9b</sup>

We have found that secondary aliphatic diazo compounds undergo rate-determining proton transfer to form alkanediazonium ions with bimolecular rate constants which can approach the diffusion-controlled limit. The major alkylating pathway involves collapse of ensuing intimate ion pairs and diffusion-controlled reactions with nucleophiles. The lifetimes of simple *sec*-alkanediazonium ions are too small, even in relatively non-nucleophilic solvents such as HFIP, to allow for diffusional encounters with DNA unless the generation of *sec*-alkanediazonium ion intermediates occurs at almost contact distances. Preassociation of the alkanediazoate precursors probably occurs and favorable  $\pi$ – $\pi$  interactions may be responsible for preassociation. Our results and interpretations are entirely consistent

(65) Glaser, R.; Horan, C. J.; Lewis, M.; Zollinger, H. *J. Org. Chem.* **1999**, *64*, 902.

(66) It is possible that the least reactive alkanediazonium ions may live long enough to allow for partial diffusional separation from the least coordinating trifluoroacetate counterion.

(67) Wurdeman, R. L.; Church, K. M.; Gold, B. *J. Am. Chem. Soc.* **1989**, *111*, 6408.

(68) (a) Singer, B. *Prog. Nucl. Acids Res. Mol. Biol.* **1975**, *15*, 219, and 330. (b) Singer, B. *Nature* **1976**, *264*, 333.

(69) Antrub, H.; Stoner, G. D. *Cancer Res.* **1982**, *42*, 1307.

with those of Fishbein and co-workers. The major fate of simple *sec*-alkanediazonium ion intermediates outside contact distances with DNA should be the reaction with water or nucleophilic residues which may lead to other types of intracellular damage. Site specificity of DNA alkylation could arise from different local environments according to DNA sequence and the degree to which that environment is solvated. It is fortuitous that simple *sec*-alkanediazonium ions and the carbocations derived from them are so short lived, given the deleterious effects of DNA alkylation.

**5. Conclusions.** Simple dialkyl carbocations, generated photochemically from oxadiazolines via alkanediazonium ions, react with TMB with rate constants of the order of the diffusion-controlled limit, and these reactions are competitive with those with solvent, bromide ion, and azide ion. The resulting cyclohexadienyl cations are UV-vis active and monitorable by UV-LFP and react much more slowly with added nucleophiles than dialkylcarbocations. We have established that TMB can be used as a kinetic probe for evaluating the lifetimes of dialkyl carbocations and rate constants for their reactions with added nucleophiles such as bromide ion and azide ion in HFIP, TFE, and MeCN. Our measurements of the lifetimes of cations **4a–d** are the first reported lifetimes of simple secondary carbocations in HFIP, TFE, and MeCN. Lifetimes and rate constants of cations **4a,d** reported here are upper limits since significant contributions from reactions within ion pairs occur. The lifetimes for cyclobutonium ion (**4b**), an intermediate common to solvolyses of cyclobutanediazonium ions and 1-cyclopropylmethanediazonium ion, and 1-cyclopropylethyl carbocation (**4c**) in HFIP and in TFE suggest that their kinetic stabilities are of the same order of magnitude as those for analogous phenyl-substituted carbocations. The incursion of ion pair chemistry in reactions of **4a,d** indicate that N<sub>2</sub> is lost from precursor alkanediazonium ions faster than diffusional separation of alkanediazonium ion–counterion pairs. Such rate constants represent upper limits for the lifetimes of alkanediazonium ions in solution. The lifetimes and rate constants of reactions of cations **4a–d** can be used to understand the carcinogenic properties of *N*-alkyl-*N*-nitrosamines. Those *N*-alkyl-*N*-nitrosamines which give rise to simple *sec*-alkanediazonium ions must do so within contact distances of DNA in order to effect alkylation of nucleotides such as guanine. DNA alkylation must occur through preassociation of precursor *N*-alkyl-*N*-nitrosamines or alkanediazoates.

**Acknowledgment.** J.P.P. and J.W. thank the Natural Sciences and Engineering Research Council of Canada for continued support. J.P.P. would like to thank Professor Bob McClelland for sharing some related results prior to publication. We thank Paul Venneri for assistance with some GC experiments. We dedicate this paper to Dr. K. U. Ingold on the occasion of his 70th birthday.

**Supporting Information Available:** Experimental details including conditions for photolysis experiments and spectroscopic data for oxadiazolines and products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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