

It also seems likely that the coordination chemistry of  $\text{CH}_3\text{Hg}^{\text{II}}$  holds the explanation for other still unexplained aspects of its behavior in biological systems. For example, some of the  $\text{CH}_3\text{Hg}^{\text{II}}$  in the blood enters the brain, the target organ in methylmercury poisoning, where it causes lysis of cells of the central nervous system.<sup>70</sup> If the biocomplexes involved can be identified, it may be possible to determine if the membrane is the primary point of attack or if lysis results indirectly by an inhibition of enzymes or other proteins whose function is essential for the integrity of the membrane. Because of the lability of  $\text{CH}_3\text{Hg}^{\text{II}}$  complexes, identification of the biocomplexes will be difficult by conventional homogenization techniques which cause disruption of subcellular compartmentalization and which thus expose the  $\text{CH}_3\text{Hg}^{\text{II}}$  to other sulfhydryl ligands. Considering the abundance of

sulfhydryl groups, there must be a high degree of selectivity in binding for  $\text{CH}_3\text{Hg}^{\text{II}}$  to be able to seek out the target molecules. For example, there is a 4800- to 8000-fold excess of sulfhydryl groups in blood at the  $\text{CH}_3\text{Hg}^{\text{II}}$  levels at which toxic symptoms first appear.<sup>70</sup> Factors giving rise to the selectivity are as yet unknown; however, the enhanced stability of the phenylalanine complex may provide a clue.<sup>30</sup> It also seems reasonable to predict that a detailed understanding of the ligand structural features which result in chelation to  $\text{CH}_3\text{Hg}^{\text{II}}$  will provide not only some insight into the apparent selectivity of the binding of  $\text{CH}_3\text{Hg}^{\text{II}}$  by bioligands but also some guidance in the design of chemotherapeutic agents for the treatment of methylmercury poisoning.

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## Vinyl Triflate Chemistry: Unsaturated Cations and Carbenes

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There are essentially four simple carbon species that are major intermediates in organic chemistry: carbanions, radicals, carbonium ions,<sup>1</sup> and carbenes (Table I). Of these four types, vinyl carbanions and radicals have long been known, and their chemistry is understood almost as well as for their saturated analogues. However, vinyl cations and unsaturated carbenes have only recently been investigated.

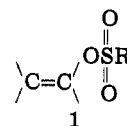
Among numerous reasons for the long delay in attention to vinyl cations and alkylidenecarbenes, two stand out: (a) vinyl cations were long regarded as unattractive reaction intermediates<sup>2</sup> because of their alleged high energy, and (b) until recently there were no good precursors for their generation. Pioneering work in the 1950s and early 1960s showed that both vinyl cations and unsaturated carbenes are energetically accessible. Hence the full development of the chemistry of these novel intermediates hinged only on the availability of simple and general progenitors.

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Table I  
Simple Reactive Intermediates of Carbon

Intermediate	Structure	Corresponding unsaturated species
Carbanion	$\text{>C}^-$	$\text{>C}=\bar{\text{C}}^-$ Vinyl anion
Radical	$\text{>C}\cdot$	$\text{>C}=\dot{\text{C}}$ Vinyl radical
Cation	$\text{>C}^+$	$\text{>C}=\text{C}^+$ Vinyl cation
Carbene	$\text{>C:}$	$\text{>C}=\text{C:}$ Methylenecarbene

It was in connection with the quest for such progenitors that vinyl sulfonate esters (1) and vinyl tri-



fluoromethanesulfonates (1, R =  $\text{CF}_3$ , triflate) attracted our attention. Trifluoromethanesulfonic acid,  $\text{CF}_3\text{SO}_3\text{H}$ , first reported by Haszeldine and Kidd,<sup>3</sup> can be manufactured by electrolysis<sup>4</sup> and is a commercially

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(2) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds", 4th ed, Wiley, New York, N.Y., 1964; Z. Rappoport and S. Patai, "The Chemistry of Alkenes", S. Patai, Ed., Interscience, London, 1964.

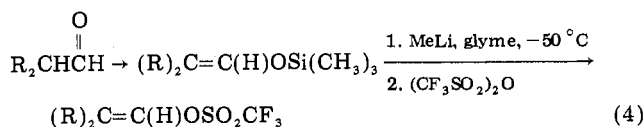
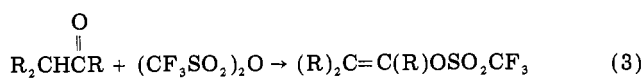
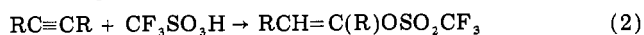
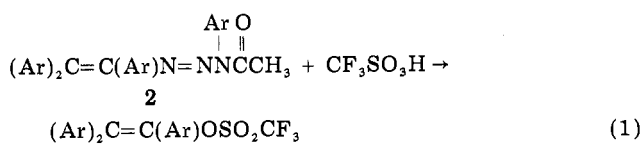
(3) R. N. Haszeldine and J. M. Kidd, *J. Chem. Soc.*, 4228 (1954).

(4) R. D. Howells and J. D. McCown, *Chem. Rev.*, **77**, 69 (1977), and references therein.

available product. Its ready availability has aided the rapid development of the chemistry of this novel acid.<sup>4</sup> Conductivity data<sup>5</sup> established  $\text{CF}_3\text{SO}_3\text{H}$  as the strongest Brønsted acid, much stronger than such common acids as  $\text{HNO}_3$ ,  $\text{H}_2\text{SO}_4$ , or even  $\text{HClO}_4$ . Hence with the exception of  $\text{N}_2$  from diazonium ions, the  $\text{CF}_3\text{SO}_3^-$  anion should be one of the best leaving groups available. Indeed it has been shown<sup>6</sup> that alkyl triflates,  $\text{ROSO}_2\text{CF}_3$ , solvolyze some  $10^4$ – $10^5$  times faster than the corresponding tosylates and therefore some  $10^8$ – $10^9$  times faster than alkyl halides.

In the 1960s little was known<sup>7</sup> about the preparation and chemistry of vinyl sulfonate esters (1) and nothing about vinyl triflates. Since then, a number of vinyl sulfonate esters such as tosylates, trinitrobenzenesulfonates, fluorosulfonates, nonafluorobutanesulfonates, and of course triflates have become available.

Vinyl triflates may be prepared by one of four ways as shown in eq 1–4. Addition of  $\text{CF}_3\text{SO}_3\text{H}$  to vinyl-



acyltriazines (2) gives good yields of vinyl triflates. However, this method is restricted by the availability of triazines and has not been widely employed. Triflic acid can also be added to alkynes or certain allenes to give moderate to good yields of vinyl triflates. This technique, however, is suitable only for preparation of disubstituted vinyl triflates with a  $\beta$  hydrogen.<sup>8</sup> The best and most general method for preparing vinyl triflates is by the interaction of enolizable ketones with the anhydride of  $\text{CF}_3\text{SO}_3\text{H}$ .<sup>9</sup> Finally, primary vinyl triflates can be made via silyl enol ethers by treating them with  $\text{CH}_3\text{Li}$  in glyme and trapping of the enolate with triflic anhydride.<sup>10</sup>

### Vinyl Cations<sup>11</sup>

Early work, involving electrophilic addition to alkynes and allenes and multiple bond participation in the

solvolytic of homopropargyl and homoallyl derivatives, established vinyl cations as viable reactive intermediates.<sup>11</sup> However, detailed investigation of their nature and behavior had to await solvolytic generation via bond heterolysis. The first solvolytic studies concerned ring-substituted bromostyrenes<sup>12a</sup> and were followed by the solvolytic generation of other stabilized vinyl cations.<sup>12b</sup> Vinyl triflates have played a key role in solvolytic studies on vinylic substrates.

### Solvolytic Displacements on Vinylic Systems.

One of the most investigated and best understood processes in organic chemistry is solvolytic displacement at saturated carbon. Recent studies<sup>13</sup> have established that vinylic solvolyses are somewhat less sensitive to solvent nucleophilicity than solvolyses at saturated carbon, are comparable in sensitivity to solvent polarity, and are rather insensitive to strong nucleophiles. Solvent  $m$  values for vinyl solvolyses<sup>13</sup> range from 0.48 to 0.85, comparable to the range observed for solvolyses of simple secondary alkyl systems like 2-propyl and 2-adamantyl tosylates. On the other hand, vinyl solvolyses are much more sensitive to the effects of substituents than saturated solvolyses with a range of Taft  $\rho^* = -4.2$  to  $-10.8$  for solvolyses of simple alkyl vinyl triflates<sup>13</sup> compared to a  $\rho^* = -3.3$  in 80% EtOH for saturated tertiary chlorides and a range of  $\rho^* = 0$  to  $-7$  for aliphatic secondary systems.<sup>13</sup> This implies a greater need for stabilization of vinyl cations which are less stable than their saturated analogues.

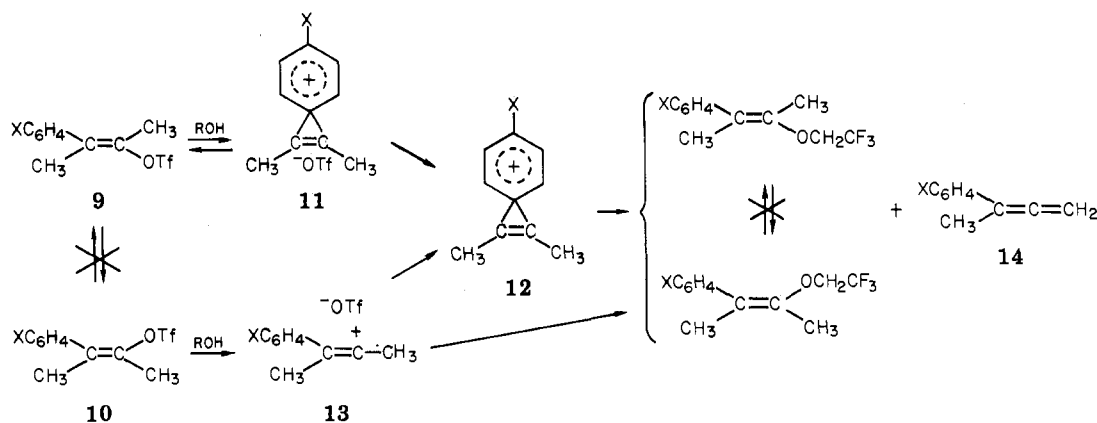
As for stereochemistry, solvolyses of isomeric (*E*)- and (*Z*)-vinyl systems show a nearly complete loss of stereochemistry in the case of aryl and cyclopropyl substituted substrates, leading to stabilized vinyl cations,<sup>12b</sup> but a significant amount of "inversion" is seen in simple alkyl vinyl systems.<sup>8b,14</sup> This "inversion" does not arise from direct  $\text{S}_{\text{N}}2$  type displacement, which is highly unfavorable in vinyl systems due to steric hindrance to in-plane backside attack,<sup>15</sup> nor from the inclusion of more favorable nucleophilic addition-elimination processes.<sup>16</sup> Rather this incomplete "inversion" is ascribed to the intermediacy of ion pairs partially protected from attack on the side of the departing nucleofugic group.<sup>8b,14</sup>

Cyclic vinyl triflates<sup>17</sup> were used to establish the linear geometry of vinyl cations, with an  $\text{sp}$ -hybridized carbon and an empty  $p$  orbital, rather than the alternative trigonal geometry with  $\text{sp}^2$  hybridization, in accord with theoretical<sup>18</sup> predictions and calculations. Medium ring ( $\text{C}_8$ – $\text{C}_{12}$ ) cycloalkenyl triflates were shown to have solvolytic behavior similar to saturated cycloalkyl systems, with the even-membered ring substrates reacting slower than the next odd-membered ring.<sup>19</sup>

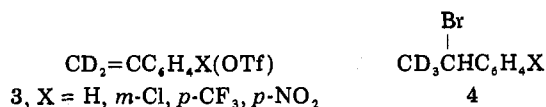
- (5) T. Gramstad, *Tidsskr Kjem, Bergves. Metall.*, **19**, 62 (1959); C. McCallum and A. D. Pethybridge, *Electrochim. Acta*, **20**, 815 (1975).  
 (6) R. L. Hansen, *J. Org. Chem.*, **29**, 4322 (1965); A. Streitwieser, Jr., C. L. Wilkins, and E. Kiehlmann, *J. Am. Chem. Soc.*, **90**, 1590 (1968); T. M. Su, W. F. Sliwinski, and P. v. R. Schleyer, *ibid.*, **91**, 5386 (1969); D. S. Noyce and J. A. Virgilio, *J. Org. Chem.*, **37**, 2643 (1972).  
 (7) P. E. Peterson and J. M. Indelicato, *J. Am. Chem. Soc.*, **90**, 6515 (1968); A. N. Nesmeyanov, et al., *Zh. Obshch. Khim.*, **29**, 2817 (1959); *Chem. Abstr.*, 12048 (1960).  
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 (9) P. J. Stang and T. E. Dueber, *Org. Synth.*, **54**, 79 (1974), and references therein.  
 (10) P. J. Stang, M. G. Mangum, D. P. Fox, and P. Haak, *J. Am. Chem. Soc.*, **96**, 4562 (1974).  
 (11) For detailed reviews see: (a) L. R. Subramanian and M. Hanack, *J. Chem. Educ.*, **52**, 80 (1975); (b) P. J. Stang, *Prog. Phys. Org. Chem.*, **10**, 205 (1973); (c) G. Modena and U. Tonellato, *Adv. Phys. Org. Chem.*, **9**, 185 (1971).

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 (14) T. C. Clarke and R. G. Bergman, *J. Am. Chem. Soc.*, **96**, 7934 (1974).  
 (15) S. I. Miller, *Adv. Phys. Org. Chem.*, **6**, 265 (1968); D. R. Kelsey and R. G. Bergman, *J. Am. Chem. Soc.*, **93**, 1953 (1971).  
 (16) Z. Rappoport, *Adv. Phys. Org. Chem.*, **7**, 1 (1969); G. Modena, *Acc. Chem. Res.*, **4**, 73 (1971).  
 (17) W. D. Pfeiffer, C. A. Bahn, P. v. R. Schleyer, S. Bocher, C. E. Harding, K. Hummel, M. Hanack, and P. J. Stang, *J. Am. Chem. Soc.*, **93**, 1513 (1971).  
 (18) J. Weber and A. D. McLean, *J. Am. Chem. Soc.*, **98**, 875 (1976), and references therein.  
 (19) R. J. Hargrove and P. J. Stang, *Tetrahedron Lett.*, **32**, 37 (1976).

Scheme I

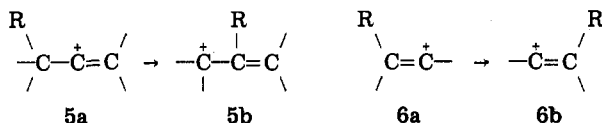


Further insight into the nature of solvolytic displacements on vinylic systems has been gained by study of kinetic deuterium isotope effects. With alkylvinyl triflates as substrates,  $\beta$ -deuterium secondary isotope effects were found in all cases to be 20–60% larger than the corresponding effects in analogous saturated substrates.<sup>20</sup> These enhanced isotope effects in vinylic substrates as compared to their saturated analogues are due to better hyperconjugative overlap, due to optimal dihedral angles<sup>21</sup> in the transition state leading to the intermediate vinyl cations, as compared to normal carbonium ions, as well as to the greater need for stabilization of these intermediates. With aryl substrates, **3**, an interesting dependence of the isotope effect upon ring substituents was observed, with  $k_{\text{H}}/k_{\text{D}}$  being 1.45 for the parent compound and 1.71 for the *p*-NO<sub>2</sub> compound. These substituent effects once again parallel the effects observed in the analogous saturated substrates<sup>21</sup> (**4**) but with a much greater magnitude for



**3** than for **4**.<sup>22</sup>

Perhaps the most characteristic reaction of carbonium ions is rearrangement, sometimes via a multitude of pathways. Vinyl cation rearrangements may be classified into two broad categories: (1) migration to the double bond (**5a** → **5b**) and (2) rearrangement



across the double bond (**6a** → **6b**). Each of these categories may be subdivided further, based upon the nature of the migrating group, into hydrogen, alkyl, or aryl migrations. Interestingly, despite the great propensity for hydride shifts in carbonium ion chemistry, for reasons not completely clear, such migrations are rare in vinyl cations with only a few known examples.<sup>23</sup>

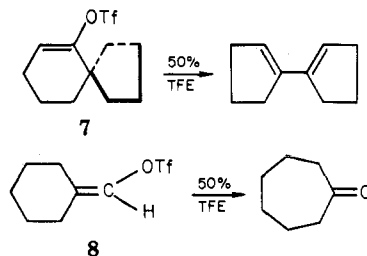
(20) P. J. Stang, R. J. Hargrove, and T. E. Dueber, *J. Chem. Soc., Perkin Trans. 2*, 843 (1974).

(21) V. J. Shiner, Jr., in "Isotope Effects in Chemical Reactions", C. J. Collins and N. S. Bowman, Ed., Van Nostrand-Reinhold, New York, N.Y., 1970, pp 90–159.

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On the other hand, there are numerous examples of alkyl migrations both to the double bond and across the double bond.<sup>11</sup> Products are generally derived from both the unrearranged and the rearranged vinyl cation with the extent of rearrangement varying with solvent nucleophilicity.<sup>11</sup> However, in the case of vinyl triflates **7** and **8** complete rearrangement was observed, strongly



suggesting a concerted ionization migration.<sup>24</sup>

An interesting system that was investigated in detail is the solvolysis of (*E*)- and (*Z*)-3-aryl-2-buten-2-yl triflates, **9** and **10**, respectively.

Deuterium labeling established<sup>25</sup> that there is extensive rearrangement in the solvolysis of both **9** and **10** in 60% aqueous ethanol. The rates for the *E* isomers, **9**, are very much faster<sup>26</sup> than the rates for the corresponding *Z* isomers, **10**, with  $\rho = -3.76$  for **9** and only  $\rho = -1.96$  for **10**. The rates of the *E* isomers deviate significantly from a plot of  $\log k$  vs.  $\sigma^*$  that includes the *Z* isomers as well as simple alkyl vinyl systems.<sup>26</sup> If the anchimerically unassisted Taft  $\rho^*$  line is taken as a measure of the unassisted rates,  $k_{\text{s}}$ , then by the well-known Winstein relationship the deviation is a direct measure of the assisted  $Fk_{\Delta}$  rate constants. Rate enhancements vary from 599 for the *p*-CH<sub>3</sub>O isomer through 68 for the parent compound to 6 for the *p*-NO<sub>2</sub> *E* isomer.<sup>26</sup> Furthermore, in absolute CF<sub>3</sub>-CH<sub>2</sub>OH the vinyl ether products from the *E* isomers **9** are highly stereoselective, with 99.85% retained stereochemistry for the *p*-CH<sub>3</sub> isomer, 99.5% for the parent, and 93.5% for the *p*-NO<sub>2</sub> isomers, respectively. Moreover, there is a good correlation between the percent of anchimerically assisted solvolysis in **9** as determined by kinetics and as measured by product stereospecificity.<sup>26</sup>

These results are rationalized by the mechanism outlined in Scheme I. Control experiments have es-

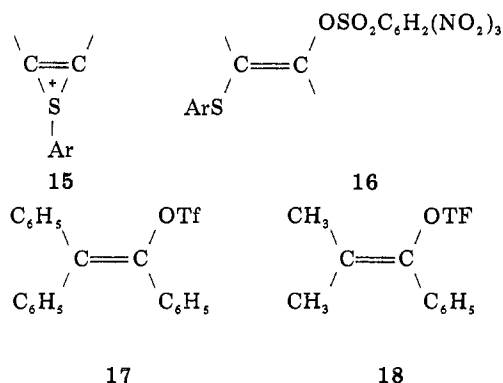
(24) P. J. Stang and T. E. Dueber, *Tetrahedron Lett.*, 563 (1977).

(25) P. J. Stang and T. E. Dueber, *J. Am. Chem. Soc.*, 95, 2683, 2686 (1973).

(26) P. J. Stang and T. E. Dueber, *J. Am. Chem. Soc.*, 99, 2602 (1977); T. E. Dueber, Ph.D. Dissertation, The University of Utah, 1974.

established that neither the starting pure isomeric vinyl triflates nor the pure isomeric vinyl ether products interconvert.<sup>26</sup> Hence, in order to account for the large anchimeric assistance, as well as the high degree of product stereoselectivity (and rearranged products), solvolyses of the geometrically favorable (*E*)-triflate **9** must proceed predominantly, if not exclusively, by a vinylidene phenonium ion. The observed internal return requires formation of an ion pair, **11**, which converts to **12** and hence into products. On the other hand, triflate **10** must initially ionize to an open linear vinyl cation pair, **13**, that can either lose a proton to give allene **14** or be preferentially captured by solvent on the side opposite the leaving group so as to form the vinyl ether products. As the triflate gegenion moves away from ion **13** and the initial unfavorable geometry is lost, it may also convert to ion **12**, partially accounting for the observed rearranged products. Vinylidene-phenonium ion **12** is of course the unsaturated analogue of the bridged phenonium ion first proposed by Cram<sup>27</sup> in the solvolyses of the isomeric 3-phenyl-2-butyl tosylates.

Further evidence for the mechanism in Scheme I is provided by the kinetic deuterium isotope effects observed in the solvolysis of appropriately labeled vinyl triflates **9** and **10**.<sup>25</sup> Similar bridged ions but with sulfur as the bridging atom, namely thiirenium ions, **15**, have



been detected by Modena and co-workers<sup>11</sup> in the solvolysis of 2-arylmercaptovinyl trinitrobenzenesulfonates **16**. On the other hand, little rearrangement was observed in the solvolyses of triarylvinyl systems, with the extent of migration being strongly dependent on the nature of the aryl groups as well as solvent polarity and nucleophilicity.<sup>28</sup> It is well established that these rearrangements proceed, as expected, by way of open linear vinyl cations with little or no anchimeric assistance.<sup>28</sup>

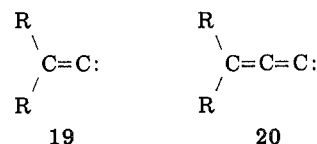
**Alkylation of Aromatic Substrates with Vinyl Triflates.** The familiar Friedel-Crafts alkylation of aromatic substrates is well established to involve electrophilic attack by carbonium ions or carbonium ion-like species.<sup>29</sup> The similarity in the solvolytic behavior of vinylic and saturated systems prompted us to inquire whether this similarity might extend to Friedel-Crafts-type alkylation with vinyl triflates. Recently we have found<sup>30</sup> that vinyl triflates that cannot

undergo elimination to acetylenes or allenes, such as triphenylvinyl triflate (**17**), 1-phenyl-2-methyl-1-propen-1-yl triflate (**18**), and cyclooctenyl and cycloheptenyl triflates, readily alkylate aromatic substrates. Alkylation occurs not only with activated substrates like anisole and toluene but also with benzene and with deactivated substrates like chloro- and fluorobenzene. Furthermore, alkylation occurs not only in the absence of a catalyst but in the presence of 4-methyl-2,6-di-*tert*-butylpyridine, a nonnucleophilic hindered base that removes the liberated triflic acid.

A careful kinetic study of the alkylation of anisole, toluene, benzene, chlorobenzene, and fluorobenzene with triflate **18** gave<sup>31</sup> a  $\rho$  value of  $-2.6$  against  $\sigma^+$ . It is instructive to compare this  $\rho$  value of  $-2.6$  with  $\rho$  values in other electrophilic aromatic substitutions such as  $-10$  for chlorinations,  $-9.1$  for acylations,  $-4.0$  for mercuration, and  $-2.4$  for ethylation.<sup>32</sup> It is obvious that the  $\rho$  value for vinyl triflate alkylations is one of the lowest observed for any electrophilic aromatic substitution. That suggests a highly reactive and intermolecularly unselective intermediate, namely a vinyl cation, for this reaction. Interestingly, we also found<sup>31</sup> the isotope effect for the competitive alkylation of  $C_6H_6$  and  $C_6D_6$  to be  $k_H/k_D = 0.98 \pm 0.02$  indicating that the rate-determining step, in analogy with normal electrophilic aromatic substitution, is not the loss of the proton from the intermediate  $\sigma$  complex.

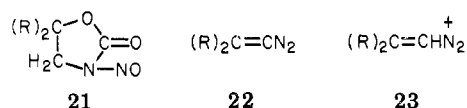
### Unsaturated Carbenes

The term unsaturated carbene properly refers to a reactive intermediate in which the hexavalent carbon is an integral part of an unsaturated system as in **19** and **20**. To date, two main classes of such species are



known:<sup>33</sup> alkylidene carbenes **19** and vinylidene carbenes **20**. This Account deals only with the former, **19**.

Alkylidene carbenes have been generated by  $\alpha$  elimination from primary vinyl halides by Hartzler<sup>33</sup> and by Kobrich and co-workers,<sup>34</sup> as well as base-promoted decomposition of *N*-nitrosooxazolidones (**21**)



as developed by Newman and co-workers.<sup>35</sup> Each of these techniques has limitations. In the case of vinyl halides the carbene-derived products generally range from 20 to 40% and the reaction probably proceeds via organometallic species and carbenoids (vide infra)

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(33) H. D. Hartzler in "Carbenes", Vol. II, R. A. Moss and M. Jones, Jr., Eds., Wiley-Interscience, New York, N.Y., 1975; P. J. Stang, *Chem. Rev.*, in press.

(34) G. Kobrich, *Angew. Chem., Int. Ed. Engl.*, **6**, 41 (1967), and references therein.

(35) M. S. Newman and A. O. Okorududu, *J. Am. Chem. Soc.*, **90**, 4189 (1968); *J. Org. Chem.*, **34**, 1220 (1969); M. S. Newman and Z. Din, *ibid.*, **38**, 547 (1973).

(27) For a review see: C. J. Lancelot, D. J. Cram, and P. v. R. Schleyer, *Carbonium Ions*, **3**, 1347 (1972).

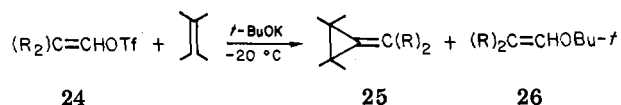
(28) Z. Rappoport, *Acc. Chem. Res.*, **9**, 265 (1976), and references therein.

(29) G. A. Olah, "Friedel-Crafts Chemistry", Wiley-Interscience, New York, N.Y., 1973.

(30) P. J. Stang and A. G. Anderson, *Tetrahedron Lett.*, 1485 (1977).

rather than free carbenes. From 21 carbene-derived products are obtained in much improved yields. However, the exact mechanism of carbene formation from 21 is complex and not well understood;<sup>36</sup> either diazoethylenes 22 or diazonium ions 23 are potential intermediates. Furthermore, the preparation of the precursor oxazolones requires several steps.

Once again we realized that a better understanding of the nature of alkylidene carbenes, 19, as well as the full development of their potential chemistry had to await the development of superior progenitors. Therefore, we turned to primary vinyl triflates 24 as



alkylidene carbene precursors and showed that, in a variety of olefins as solvents, excellent yields of carbene adducts 25 and insertion products 26 resulted upon treatment of vinyl triflates with *t*-BuOK.<sup>10</sup>

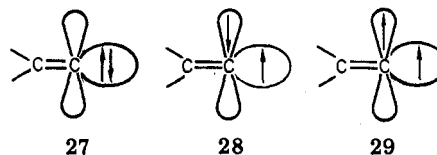
Having developed vinyl triflates as unsaturated carbene precursors, we set out to establish (a) the scope of such carbene generation, (b) the nature of triflate-derived alkylidene carbenes, and (c) the chemistry and uses of these carbenes.

**Scope of Alkylidene Carbene Generation via Vinyl Triflates.** Unlike dialkyl primary vinyl triflates, aryl- or diarylvinyl triflates yield no adducts with any olefin trap but give arylacetylenes as the sole products.<sup>10</sup> Recently, by means of <sup>14</sup>C labeling we have established that these rearrangements proceed via the intermediacy of free carbenes.<sup>37a</sup> Similar rearrangements and alkyne formation have been observed in the treatment with strong base of arylvinyl halides as well as aryl-substituted oxazolones.<sup>33</sup> It has been shown by <sup>14</sup>C labeling as well as stereochemical studies that the arylvinyl halide rearrangement does not proceed through a free carbene but rather via an organometallic and carbenoid-type intermediate.<sup>34</sup>

Base treatment of  $\beta$ -hydrogen-containing vinyl halides and vinyl triflates, as well as the parent nitroso-oxazolone, gives only alkynes, with no trace of adducts. In the cases of vinyl halides and vinyl triflates, such reactions might proceed by either a classical E2 type  $\beta$  elimination or an  $\alpha$  elimination followed by hydrogen migration. By means of deuterium labeling we found, perhaps surprisingly, that in the case of vinyl triflates reaction occurs by  $\alpha$  elimination and with the intermediacy of an alkylidene carbene, rather than by  $\beta$  elimination.<sup>37b</sup> Neither  $\beta$ -aryl- nor  $\beta$ -hydrogen-substituted alkylidene carbenes can be trapped intermolecularly in competition with their intramolecular rearrangement to give acetylenes. Therefore, only  $\beta$ -dialkyl-substituted alkylidene carbenes can be trapped with substrates and their chemistry explored.

**Nature of Alkylidene Carbenes.** The exact nature of any reactive intermediate is an interesting question. The nature of an alkylidene carbene may be defined in terms of its spin multiplicity, electrophilicity or nucleophilicity, free carbene or carbenoid character, and steric factors in its behavior.

An unsaturated carbene, as any carbene, may be in one of the three low-energy states: a singlet ( $S_0$ ) in which one carbon atomic orbital is empty and the second contains two unshared spin-paired electrons (27), a singlet ( $S_1$ ) with two singly occupied orbitals (28),



or the triplet state ( $T_1$ ) in which two electrons with parallel spins singly occupy two carbon AO's (29). Theoretical calculations<sup>38</sup> predict the  $S_0$ , 27, as the ground state for alkylidene carbenes with a singlet-triplet splitting of 20–46 kcal/mol.

Current methods of alkylidene carbene generation do not allow for ESR or CIDNP investigation of the spin multiplicity of these species. We therefore resorted to the alternative technique of examining the stereochemistry of addition<sup>39</sup> to *cis* and *trans* olefins. The addition of vinyl triflate-derived  $(\text{CH}_3)_2\text{C}=\text{C}$ : to both *cis*- and *trans*-2-butene was found<sup>40</sup> to be  $99.5 \pm 0.5$  and  $100.0 \pm 0.5\%$  stereospecific, respectively, as was addition to *cis*- and *trans*-2-methoxy-2-butene. These results strongly suggest that the nascent carbene is a singlet. Complete stereospecificity, even in the presence of an inert diluent that should facilitate intersystem crossing prior to reaction, also indicates that the ground state for alkylidene carbenes is the singlet ( $S_0$ , 27), in accordance with theoretical predictions.

The electrophilicity or nucleophilicity of alkylidene carbenes was established by examination of the relative reactivity of  $(\text{CH}_3)_2\text{C}=\text{C}$ : with a series of ring-substituted styrenes.<sup>41</sup> The vinyl triflate-derived carbene gives an excellent Hammett  $\sigma$ - $\rho$  plot for addition to styrenes, with a  $\rho$  value of  $-0.75$ . The sign and magnitude of this  $\rho$  indicate that alkylidene carbenes are mildly electrophilic and comparable in their electrophilicity to the halocarbenes  $\text{Cl}_2\text{C}$ : and  $\text{F}_2\text{C}$ :. Interestingly, both the *N*-nitrosooxazolone- and the vinyl bromide-derived alkylidene carbenes were found to be much more electrophilic, with  $\rho$  values of  $-3.4$  and  $-4.3$ , respectively.<sup>42</sup> These latter  $\rho$  values are unusually high for a neutral species like a carbene.

The degree of encumbrance and the resultant variation in properties of carbenes have long fascinated chemists. For any carbene, including unsaturated carbenes, there are two extremes: one is a carbenoid,<sup>43</sup> in which the carbene is strongly associated with the leaving group and/or the metal of the base used for its generation,<sup>43</sup> and the other a species free of any association, presumably only possible in the gas phase. Association of the leaving group would be expected to occur through the empty p orbital while association with metals would occur via the electron-rich carbenic orbital.

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## Scheme II

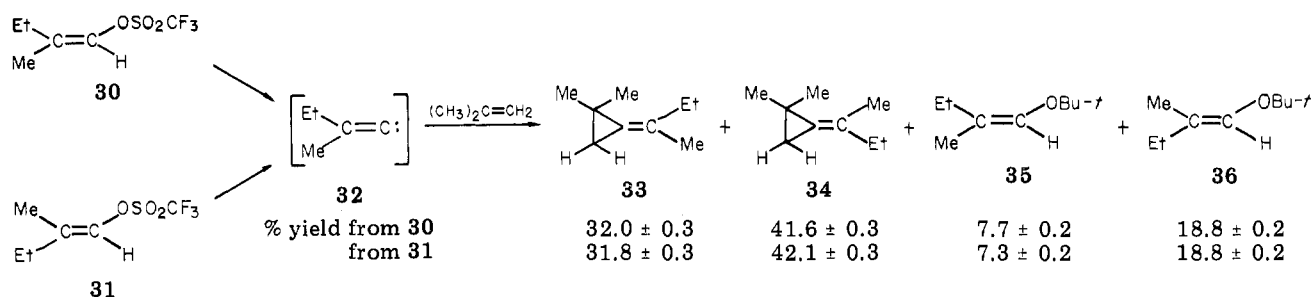


Table II  
Relative Reactivity of  $(\text{CH}_3)_2\text{C}=\text{C}:$  with Styrenes ( $\text{XC}_6\text{H}_4\text{CH}=\text{CH}_2$ )

Substrate	Reaction conditions and $k_{\text{rel}}$ (substrate/styrene)		
	$(\text{CH}_3)_2\text{C}=\text{CHOTf}$ , $t\text{-BuOK}$ , $-20^\circ\text{C}$	$(\text{CH}_3)_2\text{C}=\text{CHOTf}$ , $t\text{-BuOK}$ , $-20^\circ\text{C}$ , crown ether	$(\text{CH}_3)_2\text{C}=\text{C}(\text{H})\text{N}=\text{NSO}_2\text{C}_6\text{H}_4\text{CH}_3$ , $0^\circ\text{C}$
X = <i>p</i> - $\text{CH}_3\text{O}$	$1.51 \pm 0.02$	$1.50 \pm 0.01$	$1.51 \pm 0.10$
X = <i>p</i> - $\text{CH}_3$	$1.28 \pm 0.04$	$1.26 \pm 0.03$	$1.31 \pm 0.08$
X = H	1.0	1.0	1.0
X = <i>p</i> -Cl	$0.63 \pm 0.01$	$0.62 \pm 0.01$	$0.68 \pm 0.08$ ( <i>p</i> -Br)
Cyclohexene	$1.74 \pm 0.14$	$1.78 \pm 0.13$	$1.84 \pm 0.11$

In the case of alkylidenecarbenes, association with the leaving group may be probed by the following method. Addition of an unsymmetrical carbene, **32**, to an unsymmetrical olefin such as isobutylene results in two distinct adducts, **33** and **34**, and in the case of the vinyl triflate-derived carbene, in two distinct insertion products, **35** and **36**, as shown in Scheme II. A necessary, albeit not sufficient, condition for intermediacy of the free carbene (free of association with the leaving group) **19** is that the isomeric triflates **30** and **31** give an identical ratio of adducts as well as insertion products. To put it differently, if there is any association with the leaving group there should be a memory effect that reflects itself in the product ratio as a function of the structure of the carbene precursors. We found<sup>10</sup> that within experimental error the product ratios were identical, strongly suggesting a carbene free of association with the leaving group.

Association with the metal,  $\text{K}^+$ , in the case of triflate-generated carbene, could be probed by selectivity studies in the presence and absence of crown ethers, a technique pioneered by Moss and co-workers.<sup>44</sup> The 18-crown-6 ethers in particular would be expected to coordinate  $\text{K}^+$  much more strongly than the carbene. Recently we have employed tosylazoalkenes **40** as alkylidene progenitors and compared the selectivity of the tosylazoalkene-derived species with the selectivity of the triflate-derived species, as shown in Table II. This latter technique is particularly valuable since no metal is involved at all. The remarkable similarity of all these relative reactivities under the diverse reaction conditions precludes the association of the carbene with  $\text{K}^+$  and indicates that at least the vinyl triflate- and tosylazoalkene-derived alkylidenecarbenes are free carbenes. That is, association with the leaving group and any metals is excluded. However, any association with solvent or substrate is presently impossible to probe experimentally, as is the possibility of a very rapid equilibrium between carbenoid and free carbene with the free carbene reacting much faster.

Table III  
Relative Reactivity of Vinyl Triflate-Derived  
 $(\text{CH}_3)_2\text{C}=\text{C}:$  with Olefins<sup>45</sup>

Substrate	Rel reactivity	Substrate	Rel reactivity
Ethyl vinyl ether	2.53	1,3-Butadiene	0.30
Cyclohexene	1.00	1-Octene	0.22
<i>cis</i> -2-Butene	0.96	<i>trans</i> -2-Butene	0.18
Cyclooctene	0.88	1-Butene	0.17
Norbornylene	0.54	Isobutylene	0.11
2-Methyl-2-Butene	0.30	2,3-Dimethyl-2-butene	0.027

Table IV  
Regioselectivity of Addition of  $\text{RCH}_2\text{C}=\text{C}:$   
Unsymmetrical Olefins

R	$\text{R}_1 = \text{R}_2 = \text{CH}_3$	$\text{R}_1 = \text{H}, \text{R}_2 = t\text{-Bu}$
Et	43%	57%
<i>i</i> -Pr	40	60
<i>t</i> -Bu	33	67
Et	33	67
<i>i</i> -Pr	25	75
<i>t</i> -Bu	6	94

In contrast to the behavior of the vinyl triflate-derived carbene, there is little doubt that the vinyl halide-derived species is more of a carbenoid than free carbene. Kobrich and co-workers<sup>34</sup> have convincingly shown by means of trapping with electrophilic reagents such as  $\text{CO}_2$  and  $\text{Br}_2$  that at low temperature the reactive intermediate is in fact an organolithium compound rather than a free carbene.

Further insight into the nature of alkylidenecarbenes is gained by studies of the relative reactivity<sup>45</sup> and regioselectivity<sup>46</sup> of  $(\text{CH}_3)_2\text{C}=\text{C}:$  toward various olefins, as summarized in Tables III and IV, respectively. The relative reactivity data clearly indicate the steric re-

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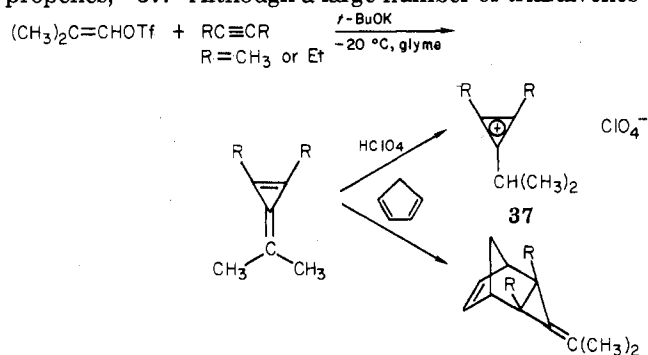
quirements of alkylidenecarbenes. Contrary to the behavior of the large majority of saturated carbenes that react faster with tetramethylethylene than with less substituted olefins, alkylidenecarbenes react much slower due to steric hindrance. In fact, all of the reactivities in Table III are accountable by the opposing effects of electronic and steric factors in the olefin in its interaction with the carbene.<sup>45</sup> The initial approach of the electrophilic carbene to the olefinic  $\pi$  system occurs via the empty p orbital of the carbene, which is constrained to be in the same plane as the  $\beta$ -alkyl substituents, thereby causing steric congestion with the substituents on the olefin.

These conclusions are reaffirmed by the regioselectivity data. The regioselectivity data<sup>46</sup> together with the observation of only 1,2 addition to *cis,trans*-1,5-cyclodecadiene<sup>47</sup> also strongly indicate a concerted carbene-olefin addition rather than a two-step process, as suggested by Newman and Patrick.<sup>48</sup>

Having established that vinyl triflate-derived alkylidenecarbenes 19 are singlets, electrophilic, and free, and that they react with definite steric requirements, we set out to explore their chemistry and potential uses.

**Chemistry of Vinyl Triflate-Derived Alkylidenecarbenes.** Vinyl triflate-derived carbenes similar to the species obtained from vinyl halides and from nitrosooxazolones 19 readily insert into both O-H and Si-H bonds.<sup>10</sup> However, to date we have found no example of C-H insertion by such carbenes. In fact, contrary to the behavior of normal carbenes, there are few examples of C-H insertion by alkylidenecarbenes.<sup>33</sup> It is possible that ordinary C-H bonds do not possess sufficient electron density for insertion to occur by the weakly electrophilic alkylidenecarbenes.

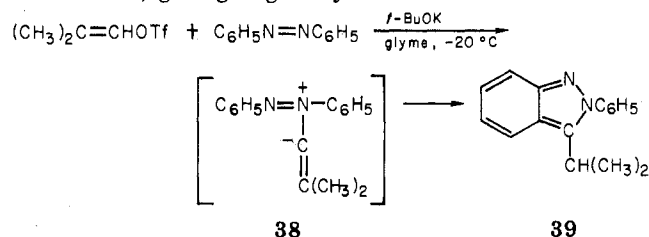
The ready addition of these carbenes to C=C bonds prompted us to investigate their addition to alkynes and thereby provide an easy route into methylenecyclopropenes,<sup>49</sup> 37. Although a large number of triafulvenes



are known, they all have strongly electron-stabilizing substituents such as CN, CF<sub>3</sub>, and COOR at the exocyclic positions and usually aryl groups on the ring.<sup>49</sup> Addition of the triflate-derived carbene provides a ready route into the in situ preparation of simple tetraalkyltriafulvenes, as shown by trapping with cyclopentadiene or HClO<sub>4</sub>.<sup>50</sup>

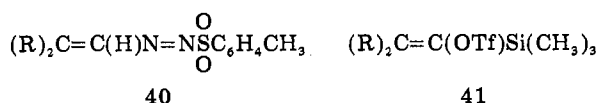
Having succeeded in the addition of the triflate-derived carbene to alkynes, we explored addition to heteronuclear multiple bonds and in particular to azo

compounds. We found<sup>51</sup> that addition to azobenzene does occur, giving a good yield of the 2-indazole 39



probably via an ylide-type intermediate, 38. This reaction represents an efficient single step entry into this interesting class of 10- $\pi$ -electron heterocyclic system.

There are also numerous substrates, for example, ketones and nitriles, to which one would like to add alkylidenecarbenes. However, these substrates are sensitive to strong bases like RLi and *t*-BuOK, and hence we have developed<sup>52</sup> two new routes for the generation of such carbenes in the absence of strong bases. One technique involves decomposition, at room temperature, of tosylazoalkenes 40, a process that re-



quires no base at all. The second involves fluoride ion-initiated  $\alpha$  elimination from silylvinyl triflates (41). This latter process is particularly valuable as it takes place at -20 to 0 °C in 1-2 h and results in nearly quantitative yields of carbene adducts.<sup>52</sup> Similar nonbasic generation of alkylidenecarbenes was previously reported<sup>53</sup> by Seyferth and Dagani and by Cunico and Han. These new techniques should greatly enhance the range of substrates and hence the uses of alkylidenecarbenes.

## Conclusion and Future Developments

We have seen that a great deal of work has been done on the chemistry of vinyl triflates despite their availability for less than a decade. They have provided a major impetus to the full development of vinyl cation and alkylidenecarbene chemistry. Yet a lot remains to be done.

In respect to vinyl cations, although some NMR spectral observations in strong acid conditions have appeared,<sup>54</sup> they are preliminary in character. Data are starting to appear on the gas-phase stability and heats of formation of vinyl cations,<sup>55</sup> but this is again only a start. Perhaps the most interesting future developments will involve the use of vinyl cations in synthesis.

In the area of unsaturated carbenes, more work clearly needs to be done in developing better techniques for photochemical generation of alkylidenecarbenes. Perhaps matrix isolation and ESR observation of such photochemically generated species will be possible. Little has been done in the area of methylenecarbenes substituted with heteroatoms such as N, O, S, F, and Br. These will be of both mechanistic and synthetic

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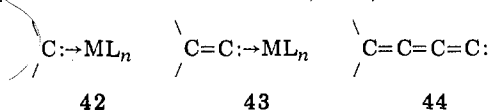
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interest for they possess added functionality and hence the potential for further synthetic manipulation. A great deal of work has been done on transition-metal complexes of normal carbenes,<sup>56</sup> 42, but unsaturated



carbene-transition-metal complexes,<sup>57</sup> 43, need further attention.

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More work will be forthcoming in the area of synthetic applications of alkylidenecarbenes, particularly in the preparation of strained small-ring compounds. Extended carbenes, such as 44 and others, and their chemistry will be explored.

Vinyl triflates will no doubt play a continuing role in some of these developments. Perhaps the greatest unrealized potential of vinyl triflates is their full development as useful synthetic reagents.

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## Structural Basis of the Activation and Action of Trypsin<sup>1</sup>

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A hundred years ago, W. Kühne first introduced the word "enzym" to describe the pancreatic protease trypsin.<sup>2,3</sup> Trypsin turned out to be an enzyme of utmost importance. It is a prominent member of a whole family of functionally and structurally related digestive enzymes. Among these are chymotrypsin and elastase, which have also been analyzed as to their three-dimensional structures.<sup>4,5</sup>

Trypsin forms the functional principle of some large and highly specific proteases involved in blood clotting<sup>6</sup> and complement binding.<sup>7</sup> Amino acid sequence studies of some of these proteases show the presence of a trypsin-like core with large segments attached to it which modify the specificity and are responsible for interaction with other macromolecules of the system.<sup>8</sup>

Most of the individual steps in the cascade reactions leading to blood clotting or complement binding are specific proteolytic cleavages liberating and activating yet another protease. Also, in this respect trypsin is a prototype as it is biosynthesized as an inactive precursor, trypsinogen, which is activated by limited proteolysis.<sup>9</sup> Limited proteolysis is also involved in phage maturation.<sup>10</sup> Limited proteolysis is indeed a most important regulatory phenomenon.

A recent fascinating finding was that some of the naturally occurring protease inhibitors are liberated from

inactive precursors (pro-inhibitors) by limited proteolysis.<sup>11</sup> This indicates the existence of a regulatory hypercycle involving proteases and their inhibitors: proteases activate, but also destroy (by proteolytic action on temporary inhibitors<sup>12</sup>) their inhibitors.

A common effector in protease action is calcium, which possibly acts by stabilizing the three-dimensional structure.<sup>13</sup> Trypsin has a well-defined calcium binding site,<sup>14</sup> and calcium influences its functional and structural properties.

Because trypsin is in so many ways a prototype, a detailed understanding of its structure and function is

(1) See IUPAC-IUB Commission on Biochemical Nomenclature, *Biochemistry*, **9**, 3471 (1970), for abbreviations. Other abbreviations used: PTI, pancreatic trypsin inhibitor (Kunitz); STI, soybean trypsin inhibitor; e, electrons; DIP, diisopropylphosphoryl; rms, root mean square;  $K_S$ , dissociation constant of the enzyme-substrate complex; conformational angles are defined according to IUPAC-IUB;<sup>1</sup> residues of the inhibitor are indicated by (I) or underlined.

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