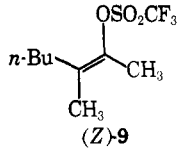
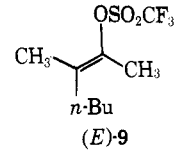

(Z)-9


(E)-9

6,7-dihydro analogs (*Z*)-**9** and (*E*)-**9**,[2] which cannot cyclize, there appears to be a significant inversion component in the solvolytic displacement reaction. Interestingly, the cyclization reaction also displays an inversion preference—more cyclization is observed in the isomer (*E*)-**3** in which the leaving group and remote double bond are trans to one another. While one might expect a similar (and perhaps even stronger) inversion preference in saturated cation cyclization systems,[1b-e] an experiment designed to determine this preference has not been reported. Once formed, the cyclized cation (whatever its structure[8]) appears to react independently of the stereochemistry of its acyclic precursor; the relative ratios of **6**, **7**, and **8** produced from (*Z*)-**3** and (*E*)-**3** are quite similar.

Because (1) both the inter- and intramolecular displacement processes are stereoselective rather than stereospecific, (2) (*Z*)-**3**, (*E*)-**3**, and their 6,7-dihydro analogs[2] react at qualitatively similar rates,[9] and (3) the cis/trans vinyl trifluoroethyl ratios are very similar to those observed[2] for (*Z*)-**9** and (*E*)-**9**, we feel that intervention of ion pairs is the most reasonable way of accounting for the results reported here.[1a,b] A mechanism is outlined in Scheme I; we assume that ion pairs (*Z*)-**10** and (*E*)-**10** undergo solvent trapping with inversion of configuration and competitive escape to the "free" ion **11**. The counterion in (*Z*)-**10** is properly oriented to prevent attack at C_2 by the remote double bond; in (*E*)-**10** this attack can occur without hindrance. This accounts for the excess cyclization observed from (*E*)-**3**. Vinyl cation **11** also gives rise to (*Z*)-**5**, (*E*)-**5**, and **12**, but its selectivity is presumably not influenced by the stereochemistry of either precursor.

Acknowledgments. We are grateful to the National Institutes of Health for financial support of this work.

(8) For convenience, a nonclassical "homoallylic" structure for cyclized cation **12** is employed in Scheme I.

(9) Half-lives for disappearance of each of the four vinyl triflates discussed have been estimated by monitoring each solvolysis by vpc. Relative rates calculated from these data are: (*Z*)-**3**, 1.0; (*E*)-**3**, 1.84; (*Z*)-**9**, 1.13; (*E*)-**9**, 2.12. The lack of evidence for concerted cyclization is consistent with the mechanism outlined in Scheme I.

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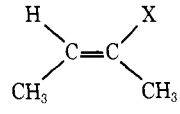
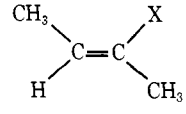
The Stereochemistry of Solvolysis of Simple Vinyl Trifluoromethanesulfonates (Triflates)

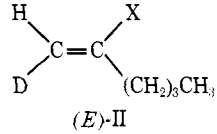
Sir:

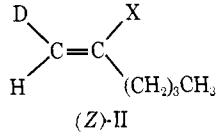
The solvolysis behavior of simple alkyl-substituted aliphatic and vinylic substrates provides an interesting contrast. Despite their lower stability relative to comparable aliphatic carbonium ions,[1] vinyl cations appear to be involved in typical solvolyses of substrates bearing only alkyl substituents.[1,2] Simple primary and secondary aliphatic substrates, on the other hand, prefer to react by SN2 or ion-pair SN2 pathways with considerable solvent assistance[3] and complete inversion.[3,4] The available evidence for a predominate SN1 rather than SN2 mechanism for alkyl vinyl solvolyses is somewhat indirect, *e.g.*, the observation of rearrangements[5a,b] and the lack of rate depressions of cycloheptenyl and cyclooctenyl triflates (relative to acyclic models), despite the impossibility of rear-side attack.[5c] Recent theoretical calculations emphasize the relative difficulty of SN2 displacements in vinyl systems.[6]

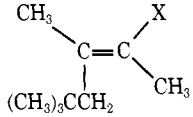
We have now studied the stereochemistry of buffered acetolysis of the (*Z*) and (*E*) isomers[7] of three simple vinyl triflate systems, I-OTf–III-OTf.[2] Although net inversion predominated in most, but not all of the cases studied, the results confirm the essential SN1 character of vinyl solvolyses.[2,5]

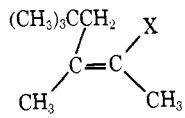

(E)-I


(Z)-I


(E)-II


(Z)-II


(E)-III


(Z)-III

The preparation of (*E*)-I-OTf and (*Z*)-I-OTf by addition of trifluoromethanesulfonic acid to 2-butyne (glc separation) has already been reported.[5d] The prepara-

(1) For recent reviews, see: M. Hanack, *Accounts Chem. Res.*, **3**, 209 (1970); H. G. Richey and J. M. Richey in "Carbonium Ions," Vol. II, G. A. Olah and P. v. R. Schleyer, Ed., Wiley, New York, N. Y., 1970, p 899; Z. Rappoport, T. Bässler, and M. Hanack, *J. Amer. Chem. Soc.*, **92**, 4985 (1970); G. Modena and U. Tonellato, *Advan. Phys. Org. Chem.*, **9**, 185 (1971).

(2) The case for vinyl cation intermediates from substrates bearing stabilizing aryl, vinyl, or cyclopropyl substituents is even stronger.[1] Stereochemical studies on such substrates have indicated that complete racemization occurs in the solvolysis of these compounds. See: (a) Z. Rappoport and Y. Apeloig, *Proc. Israel J. Chem.*, 7, 34 (1969); (b) Z. Rappoport and Y. Apeloig, *J. Amer. Chem., Soc.*, **91**, 6734 (1969); (c) D. R. Kelsey and R. G. Bergman, *ibid.*, **92**, 228 (1970); (d) D. R. Kelsey and R. G. Bergman, *ibid.*, **93**, 1941 (1971); (e) however, *cf.* G. F. P. Kernaghan and H. M. R. Hoffman, *ibid.*, **92**, 6988 (1970); (f) during the course of this work we became aware of a similar study by T. C. Clarke, D. R. Kelsey, and R. G. Bergman, *ibid.*, **94**, 3626 (1972). Triflates similar to (*E*)-III and (*Z*)-III were solvolyzed in trifluoroethanol and results analogous to those we found were obtained.

(3) See a recent review: D. J. Raber and J. M. Harris, *J. Chem. Educ.*, **49**, 60 (1972).

(4) (a) A. Streitwieser, Jr., and T. D. Walsh, *J. Amer. Chem. Soc.*, **87**, 3686 (1965); (b) A. Streitwieser, Jr., T. D. Walsh, and J. R. Wolfe, Jr., *ibid.*, **87**, 3682 (1965); (c) H. Weiner and R. A. Sneen, *ibid.*, **87**, 287 (1965).

(5) (a) A. G. Martinez, M. Hanack, R. H. Summerville, P. v. R. Schleyer, and P. J. Stang, *Angew. Chem., Int. Ed. Engl.*, **9**, 302 (1970); (b) M. A. Imhoff, R. H. Summerville, P. v. R. Schleyer, A. G. Martinez, M. Hanack, T. E. Dueber, and P. J. Stang, *J. Amer. Chem. Soc.*, **92**, 3802 (1970); (c) W. D. Pfeifer, C. A. Bahn, P. v. R. Schleyer, S. Bocher, C. E. Harding, K. Hummel, M. Hanack, and P. J. Stang, *ibid.*, **93**, 1513 (1971); (d) P. J. Stang and R. H. Summerville, *ibid.*, **91**, 4600 (1969).

(6) P. R. Kelsey and R. G. Bergman, *ibid.*, **93**, 1953 (1971).

(7) J. E. Blackwood, C. L. Gladys, K. I. Loening, A. E. Petrarca, and J. E. Rush, *ibid.*, **90**, 509 (1968).

Table I. Solvolysis Products of Vinyl Triflates in NaOAc-Buffered Acetic Acid, 100°

Compound	Normalized product composition, %[a] Acetylene	Allene	Ret OAc	Inv OAc	Acetate, % inversion
(*Z*)-I-OTf[b]	95.3 ± 0.2		1.95 ± 0.2	2.7 ± 0.2	58.2 ± 0.2[c]
(*E*)-I-OTf[b]	77.5 ± 0.5	4.7 ± 0.2	1.0 ± 0.1	16.8 ± 0.1	94.4 ± 0.5[c]
II-OTf[d]	61.7 ± 0.1	18.5 ± 0.4	18.0 ± 0.5		
(*Z*)-II-OTf (74 ± 3%)[d,e]	57.3 ± 0.2	22.5 ± 0.5	17.6 ± 0.2 (68 ± 3% (*E*)-II-OAc)[e]		92 ± 8
(*E*)-II-OTf (77 ± 3%)[d,e]	62.4 ± 0.1	20.7 ± 0.1	16.0 ± 0.2 (68 ± 3% (*Z*)-II-OAc)[e]		88 ± 8
(*Z*)-III-OTf[b,f]		42.2	6.0	52.4	89.7
		36.3	7.0	56.3	88.9
(*E*)-III-OTf[b,f]		57.4	24.1	18.5	43.4
		49.3	30.0	21.6	41.6

[a] Glc areas corrected for experimentally determined response factors. Product error limits are average deviations between duplicate runs except with (*Z*)-I-OTf which was determined in triplicate. [b] Triflate 0.06–0.1 *M*, NaOAc 0.11 *M*. [c] Inversion percentages were calculated *for each run*. The error limits quoted are average deviations between values for different runs. [d] Triflates 0.5 *M* in CH_3COOD, 1.3 *M* in NaOAc. The remainder of the product was 2-hexanone, 1–3%. With 0.11 *M* NaOAc, II-OTf gave 20.4 ± 0.1% 2-hexanone. [e] Per cent of isomer shown in mixture of both (*Z*) and (*E*) isomers determined by nmr. See ref 8 for triflates. For acetates, vinyl multiplets were integrated at (benzene solution) δ 4.34 trans and 4.56 cis to acetoxy. See H. O. House and V. Kramar, *J. Org. Chem.*, **28**, 3362 (1963). Nmr error limits assumed; actual multiple integration gave reproducibilities of ±1%. [f] Results for two individual runs given separately.

tion of (*E*)-II-OTf and (*Z*)-II-OTf was based on the similar addition of triflic acid to an excess of 1-hexyne in pentane at −30°; in the parent case a 70% yield of hex-1-en-2-yl triflate[8] resulted. The addition product of CF_3SO_2OD was shown by nmr to be mainly (*Z*)-II-OTf, with 74 ± 3% deuterium cis to the triflate group. When CF_3SO_3H was added to 1-hexyne-*1-d*, (*E*)-II-OTf resulted with 77 ± 3% deuterium trans to the triflate group. Thus, in both cases cis addition predominated. 3,5,5-Trimethyl-2-hexanone[9] was converted to a mixture of (*E*)-III-OTf and (*Z*)-III-OTf by the action of triflic anhydride in pentane in the presence of excess sodium carbonate.[10] The stereochemistry of (*E*)-III and (*Z*)-III (triflates and acetates) was assigned on the basis of differences in the chemical shifts of the β-CH_3 groups[5d,11] and in the homoallylic coupling constants,[12] these being larger when the methyl groups are trans (*e.g.*, $J_{CH_3\cdots CH_3}$ = 1.4 ± 0.1 Hz in (*E*)-III-OTf and 1.0 ± 0.1 Hz in (*Z*)-III-OTf).

Solvolysis product studies were carried out in NaOAc-buffered acetic acid at 100°. Under these conditions the vinyl acetates (*Z*)-I-OAc, (*E*)-I-OAc, (*Z*)-III-OAc, and (*E*)-III-OAc were stable toward stereomutation, and were only slowly converted to the corresponding ketones. The elimination products did not react under these conditions, nor did the starting materials isomerize. (*Z*)-II-OAc and (*E*)-II-OAc were less stable when only a slight excess of buffer was present, and were converted to 2-hexanone about twice as fast as they were formed *via* solvolysis. The products from (*Z*)-II-OTf and (*E*)-II-OTf therefore were studied in $DOOCCH_3$ 1.3 *M* in NaOAc (saturated at 25°). The use of $DOOCCH_3$ decreased the rate of formation of 2-hexanone threefold due to the isotope effect in the rate-limiting vinyl acetate protonation. The higher concentration of NaOAc also decreased the rate of destruction of hex-1-en-2-yl acetate by a factor of about 2 while increasing the rate of solvolysis by about 1.5. The total effect of using CH_3COOD saturated with NaOAc was to decrease the rate of destruction of II-OAc by a factor of six.

The product compositions are summarized in Table I. Elimination is always important and usually predominates. This was especially true with (*Z*)-I-OTf, where acetate was only 4.6% of the product, increasing the uncertainty in that case. (*Z*)-I-OTf possesses a hydrogen trans to the leaving group and a β-methyl group. Both these features favor concerted elimination, which appears to compete with SN1–E1-type solvolysis.[5d] Inverted acetate product dominated strongly from the solvolyses of (*E*)-I-OTf, (*E*)-II-OTf, (*Z*)-II-OTf, and (*Z*)-III-OTf, and averaged over 90% for these substrates. (*E*)-III-OTf, on the other hand, gave acetate only 42% inverted; the bulky neopentyl group evidently blocked rearward attack somewhat in this instance. Although free carbonium ions are excluded, these results are consistent with the other evidence indicating a cationic mechanism for alkyl-substituted vinyl solvolyses, at least for the substitution component.[5] Although inversion tends to predominate, it is not exclusive, as is the case in simple primary and secondary aliphatic systems.[4] Although we have no explicit evidence for their intervention, ion pairs are conceptually attractive intermediates enabling the rationalization of the results. Attack from the rear of such ion pairs would normally be expected, unless prevented by an adjacent bulky group. However, even (*E*)-II-OTf and (*Z*)-II-OTf, lacking β substituents, still give ~10% retention, a result inconsistent with an SN2 process. However, it is equally clear that free classical carbonium ions do not intervene. In that case, similar acetate product ratios would be expected from *E* and *Z* starting materials.

Reactions involving vinyl cations cations more nearly in a "free" state or with longer lifetimes than those

(8) Nmr (CCl_4) δ 0.98 (m, 3, CH_3), 1.50 (m, 4, CH_2CH_2), 2.37 (m, 2, allylic CH_2), 4.92 (d, 1, vinyl CH trans to the triflate group), and 5.06 (d, 1, vinyl CH cis to the triflate group). The stereochemistry of the vinylic hydrogens was assigned by their chemical shifts; see S. W. Tobey, *J. Org. Chem.*, 34, 1281 (1969).

(9) Prepared by addition of *tert*-butylmagnesium chloride to 3-methyl-3-buten-2-one in the presence of cuprous bromide. See L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 165.

(10) General procedure: T. E. Dueber, P. J. Stang, W. D. Pfeifer, R. H. Summerville, M. A. Imhoff, P. v. R. Schleyer, K. Hummel, S. Bocher, C. E. Harding, and M. Hanack, *Angew. Chem., Int. Ed. Engl.*, 9, 521 (1970). Repeated separation by glc (15 ft × 3/8 in. column of 20% Carbowax 20M on Chromosorb W, 75°) gave (*Z*)-III [nmr (CCl_4) δ 0.93 (s, 9, *tert*-butyl), 1.80 (q, 3, β-CH_3), 2.08 and 2.13 (m, 5, CH_2 and α-CH_3)] and (*E*)-III [nmr δ 0.98 (s, 9, *tert*-butyl), 1.85 (q, 3, β-CH_3), and 2.03 (m, 5, CH_2 and α-CH_3)].

(11) There is an upfield shift of 0.10–0.15 ppm for a methyl group cis to an acetoxy relative to one cis to another methyl group. For examples, see (a) ref 2d; (b) W. E. Parham and J. F. Dooley, *J. Org. Chem.*, 33, 1476 (1968).

(12) For a review of homoallylic coupling, see S. Sternhell, *Rev. Pure Appl. Chem.*, 14, 15 (1964).

generated by solvolysis give stereochemical results which differ from those we have found.[2] Although trans additions to acetylenes have frequently been explained by ion-pair mechanisms,[13] trans addition is not the inevitable pathway, as illustrated by the CF_3SO_3D addition to 1-hexyne, described above. Peterson and Duddey[14] have shown that trifluoroacetic acid adds to 3-hexyne at 60° to give nearly equal amounts of (*E*)- and (*Z*)-hex-3-en-3-yl trifluoroacetates. We have studied the addition of trifluoroacetic acid to 2-butyne and to 1,2-butadiene at 75°. In both cases (*E*)-II-$OOCCF_3$ predominated over (*Z*)-II-$OOCCF_3$ by a ratio of 3.3. An even more striking stereochemical preference for the attack of the but-2-en-2-yl cation cis to the β-methyl group has been observed with carbon monoxide in superacid.[15]

The buffered acetolyses of alkyl-substituted vinyl triflates tend to proceed with predominate, but not exclusive, inversion in the substitution products. We conclude that ion-pair SN1 mechanisms with the leaving group blocking the front side probably best account for these results.

Acknowledgments. This work was supported by grants from the National Science Foundation, the Petroleum Research Fund, administered by the American Chemical Society, and Hoffmann-La Roche, Nutley, N. J. The program of research in vinyl triflates at Princeton has benefited from collaborative effects with Professor P. J. Stang, Utah, and Professor M. Hanack, Saarbrücken. We thank Dr. R. L. Hansen of the 3M Company for samples of trifluoromethanesulfonic acid, and Professor R. G. Bergman for his comments.

(13) R. C. Fahey, *Top. Stereochem.*, 3, 237 (1968).
(14) (a) P. E. Peterson and J. E. Duddey, *J. Amer. Chem. Soc.*, 85, 2865 (1963); (b) P. E. Peterson and J. E. Duddey, *ibid.*, 88, 4990 (1966).
(15) H. Hogeveen and C. F. Roobeck, *Tetrahedron Lett.*, 3343 (1971).
(16) National Science Foundation Predoctoral Fellow, 1969–1972.

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Plant Antitumor Agents. IX. The Total Synthesis of *dl*-Camptothecin[1]

Sir:

In 1966 a communication from this laboratory described the isolation and structure of a novel alkaloid camptothecin (**1**).[2] Initial promising reports of excellent antitumor activity[2,3] and encouraging clinical data[4,5] have stimulated wide interest in the synthesis of comptothecin and analogous compounds.[6] These efforts have culminated in two recent reports of the total synthesis of camptothecin.[7,8] We wish to report at this time an independent synthesis based on rather different principles. Some features of this synthetic procedure are also adaptable to the preparation of camptothecin analogs.[9]

The key step in our approach involves the Michael condensation of 1,3-dihydro-2-methoxycarbonyl-2*H*-pyrrolo[3,4-*b*]quinoline (**2**) with methyl 3-methylene-2-methoxycarbonyl-4-oxohexanoate (**3**).[9] The compound **2**[10] (mp 185–186°) was prepared in quantitative yield by the reaction of the corresponding amine[11] with methyl chloroformate in dilute sodium carbonate solution.

The Michael condensation[12] of **2** and **3** at 110° without added catalyst gave **4** as a viscous oil (81%) after chromatography on silica gel. Introduction of the additional carbon atom needed for the elaboration of ring E of camptothecin and protection[13] of the ketone function were achieved in one step by the reaction of **4** with liquid hydrogen cyanide in the presence of a catalytic amount of potassium cyanide. The intermediate cyanohydrin spontaneously lactonized to give a mixture[14] of isomeric cyano lactones **5** in 82% yield. Treatment of **5** with methanolic hydrogen chloride (25°, 2 days) gave the amide **6** as a mixture of diastereomers[13,14] in 76% yield.

The next crucial step involved the selective removal of the *N*-carbomethoxy function in the presence of the sensitive amide and ester functions in **6** in order to construct the D ring of camptothecin. Hydrogen bromide in glacial acetic acid has been used for the selective removal of an *N*-carbobenzyloxy group without affecting an amide or ester function in peptides.[15] It was felt that the *N*-carbomethoxy group could also be removed under these conditions without affecting the ester and amide functions in **6**. Selective removal of the *N*-carbomethoxy group could indeed be accomplished by the treatment (25°, 18 hr) of **6** with glacial acetic acid saturated with hydrogen bromide. Basification (pH 8) of the dihydrobromide of **7** with sodium methoxide in methanol at 0° followed by refluxing (4 hr) in benzene yielded a mixture of lactams **8** (17%, mp 289–290°) and **9** (32%, mp 220–223°) separable by preparative tlc. The latter could be lactonized in nearly quantitative yield by refluxing (6 hr) in benzene in the presence of half its weight of *p*-toluenesulfonic acid.

(1) Previous paper in this series: M. C. Wani, H. L. Taylor, M. E. Wall, P. Coggon, and A. T. McPhail, *J. Amer. Chem. Soc.*, 93, 2325 (1971).
(2) M. E. Wall, M. C. Wani, C. E. Cook, K. H. Palmer, A. T. McPhail, and G. A. Sim, *ibid.*, 88, 3888 (1966).
(3) For a review article describing the antitumor and antileukemic activity of camptothecin and a number of its derivatives *cf.* M. E. Wall, Abstracts, 4th International Symposium on the Biochemistry and Physiology of Alkaloids, Halle, DDR, Academic Press, Berlin, 1969, p 77.
(4) J. A. Gottlieb, A. M. Quarino, J. B. Call, V. T. Oliverio, and J. B. Block, *Cancer Chemother. Rep.*, 54, 461 (1970).
(5) Subsequent clinical studies carried out under the sponsorship of Drug Research and Development, National Cancer Institute, National Institutes of Health, have proved considerably less encouraging but full studies of this compound have been hampered because of the limited availability of camptothecin from natural sources.
(6) For a complete listing of all the publications in this field see ref 7.
(7) R. Volkmann, S. Danishefsky, J. Eggler, and D. M. Solomon, *J. Amer. Chem. Soc.*, 93, 5576 (1971).
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(12) M. C. Wani, J. A. Kepler, J. B. Thompson, M. E. Wall, and S. G. Levine, *J. Chem. Soc. D*, 404 (1970).
(13) Generation of the free amine in the presence of the keto group of 4 or the cyano group of **5** led to undesired side reactions.
(14) A preparative tlc of this mixture yielded two products. The high-resolution mass spectra, combustion analyses, ir, and uv spectra of both these products were consistent with their formulation. However, these products still appear to be mixtures of diastereomers on the basis of their complex nmr spectra and melting point behavior.
(15) R. A. Boissonnas, *Advan. Org. Chem.*, 3, 159 (1963).