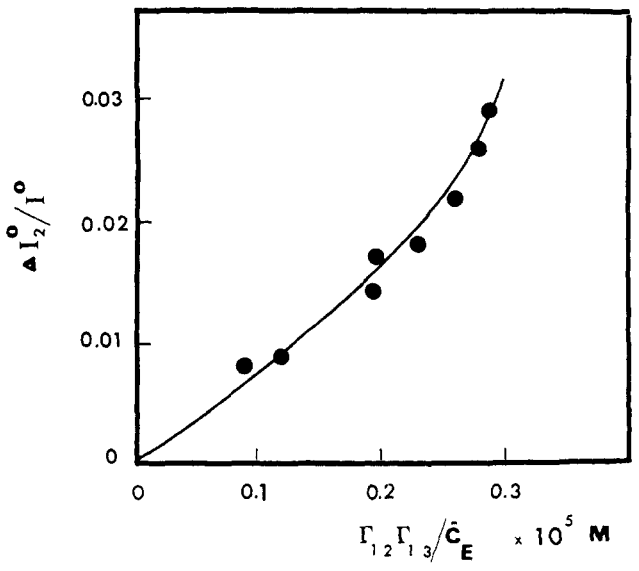

Figure 3. Concentration dependence of the relaxation amplitudes for the binding of benzamidine to trypsin. The solid line was calculated from eq 8 using values for the specific rate constants, equilibrium constants, $\Delta\epsilon_{12}$, and ΔH_{12} given in the text, and assuming $\Delta H_{13} = -4.5$ kcal/mol. Calculations were facilitated by programming the procedure for a Wang electronic calculator.

Addition of benzamidine to solutions of proflavin and trypsin resulted in the appearance of a second, slower relaxation effect, associated with an increase in OD_{469}. In Figure 2 the reciprocal relaxation times of the slow effect are plotted according to eq 5. From the best straight line through the data points we calculate $k_{13} = 2.9 \times 10^7\ M^{-1}\ sec^{-1}$ and $k_{31} = 6 \times 10^2\ sec^{-1}$. Although the experimental τ's were the same order of magnitude, substitution of the $\bar{c}$'s and four experimental k's into eq 4 reproduced the relaxation times to ± 10–20%, justifying the use of eq 5 as a first approximation.

The results of the amplitude analysis for the slow relaxation process are presented in Figure 3. In the present work, equilibrium concentrations were such that the quantity $(1 - \beta\Gamma_{12}/\bar{c}_E)/(1 - \Gamma_{12}\Gamma_{13}/\bar{c}_E^2)$ was close to unity (assuming $\beta \gtrsim 1$). From eq 9 a plot of $\delta I_2^0/I^0$ *vs.* $\Gamma_{12}\Gamma_{13}/\bar{c}_E$ should then be approximately linear. However, calculations suggest that the upward trend in Figure 3 is genuine and arises from coupling between the two steps. A good fit to the data was obtained using the *general* expression of eq 8 and assuming $\Delta H_{13} = -4.5$ kcal/mol. The uncertainty in this figure is probably about ± 1.5 kcal/mol.[16]

The enthalpies[19] and specific rate constants[20] evaluated here are consistent with simple ligand binding processes. It is emphasized, however, that we have assumed the simplest mechanism consistent with the majority of the data. In particular, the path I + EP $\rightleftarrows$ EI + P could play a minor, but significant role. Experiments dealing with this point and applications of the method to other systems are now under way.

(16) Coupling to rapid protolytic equilibria must be considered when interpreting amplitude data for enzyme reactions. However, the fact that the equilibrium constants for the proflavin–α-chymotrypsin[17] and benzamidine–trypsin[18] complexes are constant between pH 7 and 8 suggests that protolytic reactions are not important in the present study.

(17) G. Feinstein and E. Feeney, *Biochemistry*, **6**, 749 (1967).

(18) E. J. East and C. G. Trowbridge, *Arch. Biochem. Biophys.*, **125**, 334 (1968).

(19) J. L. Webb, "Enzyme and Metabolic Inhibitors," Vol. I, Academic Press, New York, N. Y., 1963, Chapters 6 and 15.

(20) G. G. Hammes, *Accounts Chem. Res.*, **1**, 321 (1968).

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A Remarkably High Stereoselectivity in the Addition of Acetic Acid and Trifluoroacetic Acid to Norbornene. Evidence for the Capture of the Norbornyl Cation in an Unsymmetrical State

Sir:

The addition of acetic acid at 100° and of trifluoroacetic acid at 0° proceeds to give the *exo*-norbornyl esters in stereochemical purities of 99.98%. Such exceptionally high stereoselectivities have been considered to require the symmetrically σ-bridged nonclassical norbornyl cation as an intermediate. Yet the distribution of the deuterium atom in the addition of the respective deuterio acids does not correspond to that required by a reaction proceeding through such a symmetrical intermediate.

The addition of acetic acid to norbornene proceeds slowly at 100° to give 2-norbornyl acetate with a remarkably high exo stereoselectivity: 99.97% exo in the absence of sodium acetate and 99.99% exo in the presence of sodium acetate.[1,2] This stereoselectivity is comparable to (actually slightly higher than) the value realized, 99.95% exo in the acetolysis of *exo*-norbornyl tosylate at 100° in the presence of 0.6 *M* sodium acetate.[4–6]

Such an extraordinarily high stereoselectivity has been considered previously to require the intermediacy of a σ-bridged cation.[7] On this basis, the addition of deuterioacetic acid to norbornene should proceed with an equal distribution of the deuterium tag between the exo-3 and syn-7 positions (eq 1). However, this does not occur.

Under the conditions of the previous study acetic acid-d_4 adds to norbornene to yield 2-norbornyl-*d* acetate-d_3 of the same high exo stereoselectivity.[8] The product was converted to *exo*-norbornanol-*d* (**1**) with

(1) Both esters are stable to the reaction conditions.

(2) The rate of addition was 2.8 times faster than that of the corresponding addition to 7,7-dimethylnorbornene.[3]

(3) H. C. Brown, J. H. Kawakami, and K.-T. Liu, *J. Amer. Chem. Soc.*, **92**, 3816 (1970).

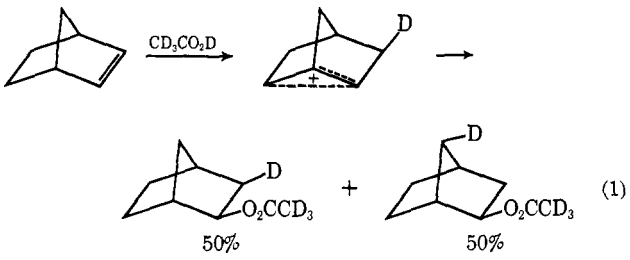
(4) Analyzed by glpc using 150 ft × 0.01 in. TCEP column at 70° on a Perkin-Elmer Model 226 gas chromatograph.

(5) Dr. Charles B. Schewene carried out independent analyses at the University of Wisconsin. Excellent agreement was realized between the two sets of analysis. We are grateful for his generous assistance.

(6) See also H. L. Goering and C. B. Schewene, *J. Amer. Chem. Soc.*, **87**, 3516 (1965).

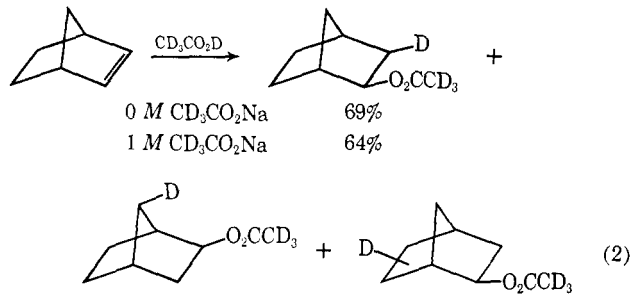
(7) S. Winstein, E. Clippinger, R. Howe, and E. Vogelfanger, *ibid.*, **87**, 376 (1965).

(8) The rate of addition is approximately one-half that observed for normal acetic acid.



50% 50% (1)

lithium aluminum hydride. Pmr analysis of **1** revealed that the product has far more deuterium at the exo-3 than at the syn-7 position (eq 2).[9,10]



0 *M* CD_3CO_2Na 69%
1 *M* CD_3CO_2Na 64%

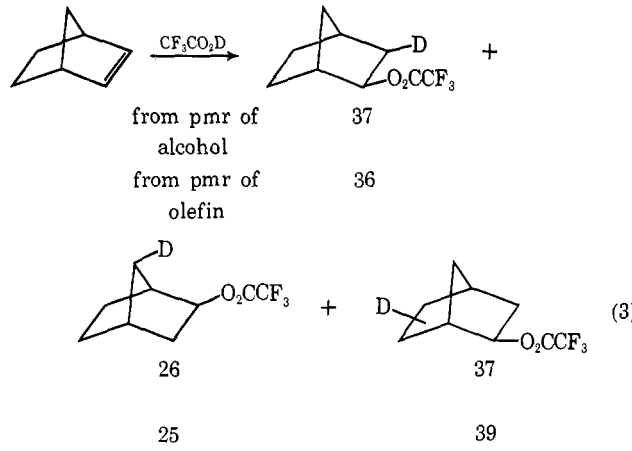
19% 12%
21% 15% (2)

In contrast to the slow addition of acetic acid to norbornene at 100°, the addition of trifluoroacetic acid to this olefin is exceedingly rapid at 0°, the reaction being complete in 1–2 min. However, here also the product is highly stereoselective, consisting of 99.98% of *exo*- and 0.02% of *endo*-norbornyl trifluoroacetate.[1,11]

The addition of deuteriotrifluoroacetic acid also exhibits the same high stereoselectivity.[1] Even more significant, the deuterium tag is not equally distributed between the exo-3 and syn-7 positions, clearly indicating an unsymmetrical structure of the reaction intermediate in this typical carbonium ion reaction.[13]

The product, *exo*-norbornyl-*d* trifluoroacetate, was converted to *exo*-norbornanol-*d* (**2**) with lithium aluminum hydride. Pmr analysis of **2** indicated 37% of exo-3-*d*, 26% of syn-7-*d*, and a considerable quantity of hydride-shifted products[14] (eq 3).

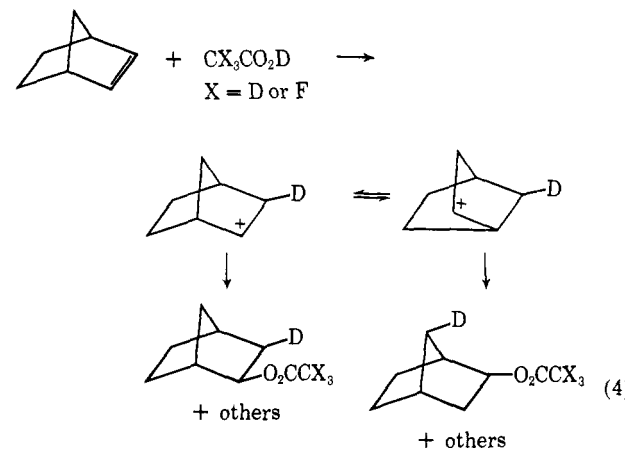
Again, the accuracy of this analysis was confirmed by converting the alcohol to the tosylate, followed by elimination to the olefin.[15,16]



26 37 (3)

25 39

These results do not appear to be explicable in terms of a mechanism proceeding through the symmetrical nonclassical norbornyl cation as sole intermediate. They can be rationalized in terms of a rapidly equilibrating pair of classical cationic intermediates which are captured before they have been fully equilibrated (eq 4).



+ others + others (4)

In terms of this interpretation, the greater amount of scrambling and hydride-shifted products in the reaction with trifluoroacetic acid could be attributed to the lower nucleophilicity of the acid, resulting in a longer lifetime for the cationic intermediate.

Alternatively, it is possible to interpret the results in terms of two distinct, competing mechanisms—an ionic addition involving a nonclassical cation and yielding product with equal distribution of the deuterium between the exo-3 and syn-7 positions, and a concerted cyclic cis addition[17,18] which places the tag exclusively at the exo-3 position. On this basis, it might be argued that approximately 50% of the addition of acetic acid to norbornene proceeds through such a concerted process and 50% proceeds through the symmetrical norbornyl cation.

This interpretation requires that the exo stereoselectivity of the postulated concerted addition process be comparable to that realized in the carbonium ion pathway. Adoption of this position would negate the argument

(9) The pmr spectra were taken with a Varian A-60A spectrometer using a 1 *M* solution of **1** in 95% pyridine–5% deuterium oxide with tetramethylsilane as internal reference. The deuterium distribution was determined by the analysis of the shape of the α-methine proton signal at δ 3.89, and by measuring the relative area of the syn-7 proton at δ 1.88. For details, see K.-T. Liu, Ph.D. Thesis, Purdue University, 1968. The reliability of the analysis was confirmed through a 60-MHz pmr study of the E2 elimination product from the corresponding tosylate (*vide infra*), and by a 100-MHz pmr study of **1**. We are grateful to Professor L. M. Stock of the University of Chicago for making available a Varian HA-100 spectrometer for this study.

(10) No correction was made for the 97–98% isotopic purity of the deuterated acid.

(11) The glpc analysis used a 50 ft × 0.02 in. tricresyl phosphate column at 100° on a Perkin-Elmer Model 226 gas chromatograph. Both isomers were synthesized from the corresponding alcohols utilizing Peterson's procedure[12] to permit direct comparison.

(12) P. E. Peterson, *J. Amer. Chem. Soc.*, **82**, 5834 (1960).

(13) P. E. Peterson, *et al.*, *ibid.*, **89**, 5902 (1967), and previous papers in this series.

(14) The formation of large amounts of hydride-shifted products was previously observed in the addition of trifluoroacetic acid under these conditions to 7,7-dimethylnorbornene.[3]

(15) The pmr study of this norbornene product was carried out with a Varian A-60A spectrometer using a 10% deuteriochloroform solution. The signals were assigned following K. Tori, *et al.*, *Can. J. Chem.*, **42**, 926 (1964); *Tetrahedron Lett.*, 9 (1966).

(16) H. C. Brown and K.-T. Liu, *J. Amer. Chem. Soc.*, **92**, 200 (1970).

(17) E. Vogelfanger, Ph.D. Thesis, University of California, Los Angeles, Calif., 1963. For a related study involving benzonorbornadiene, see S. J. Cristol and R. Caple, *J. Org. Chem.*, **31**, 2741 (1966).

(18) R. C. Fahey, *Top. Stereochem.*, **3**, 253 (1969).

that the observed unusually high stereoselectivity, 99.98% exo, is explicable only in terms of the unique stereochemical requirements of a σ-bridged intermediate.[6,7]

Evidence was previously presented that the presence of 7,7-dimethyl substituents in norbornene either forces such concerted cis additions to go preferentially endo, or prevents such additions from occurring.[19] Both acetic acid and trifluoroacetic acid readily add to 7,7-dimethylnorbornene at rates not very different from those exhibited by norbornene itself to give stereoselectively exo-cis addition products.[3] Consequently, the postulate of competing concerted cis additions of acetic acid and trifluoroacetic acid appears highly improbable.

There is a third possibility to consider. It could be assumed that the transfer of the proton from these acids to norbornene proceeds to the initial formation of the classical norbornyl cation. This cation then undergoes a closure to the nonclassical cation at a rate that is competitive with the capture of the nucleophile.[20] Thus, in the case of acetic acid, 40% of the product (nonhydride shifted) would be formed *via* the σ-bridged intermediate and 50% *via* the classical norbornyl cation captured prior to the conversion to the nonclassical ion. This mechanism could account for the isotopic distribution (eq 2). However, it requires that capture of the nucleophile by the classical norbornyl cation must proceed with stereoselectivity of essentially 99.98% exo. This again would be incompatible with the argument that such a high stereoselectivity is inexplicable save in terms of the unique steric requirements of a σ-bridged cation.[6,7]

These considerations suggest that the simplest, most consistent interpretation of these addition reactions[21] is that they proceed through rapidly equilibrating classical norbornyl cations and that such cations react with nucleophiles with a high preference for exo capture. It follows that the high stereoselectivity observed in the acetolysis of norbornyl derivatives cannot be used to support the proposal that such solvolyses proceed with σ bridging.

(19) H. C. Brown and J. H. Kawakami, *J. Amer. Chem. Soc.*, **92**, 201 (1970).

(20) Such a mechanism has been proposed to account for the formation of *exo*-norbornanol with 10% retention of optical activity in the elimination of optically active *exo*-norbornylamine: E. J. Corey, J. Casanova, Jr., P. A. Vatakencherry, and R. Winter, *ibid.*, **85**, 169 (1963).

(21) Including the addition of deuterium chloride previously studied: H. C. Brown and K.-T. Liu, *ibid.*, **89**, 466, 3898, 3900 (1967).

(22) (a) To whom correspondence should be addressed. (b) Graduate assistant on a grant (GP 6492X) provided by the National Science Foundation.

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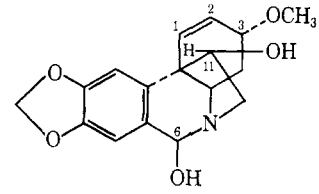
Stereospecific Synthesis of Haemanthidine and Tazettine

Sir:

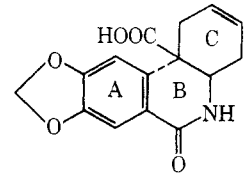
Most of the large family (>70 members) of alkaloids of the *Amaryllidaceae* belong to one of two biosynthetically related structural groups, characterized by the skeletons of lycorine and crinine.[1] The most productive synthetic challenge of the latter group appeared to be the most complex, *i.e.*, haemanthidine (**1**),



1

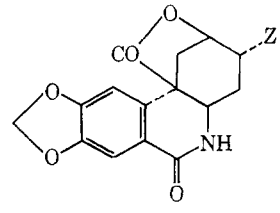
since removal of the functions at C-6 and C-11 (and alteration at C-3) should concurrently afford easy routes to many of the simpler members, while syntheses of the latter do not so readily also lead to haemanthidine. There is further synthetic challenge in the stereochemical control of five asymmetric centers and the reactivity of haemanthidine to both mild acids and bases.

A system for synthesis design[2] reveals that creation of quaternary carbons is the most limited construction operation. We selected cycloaddition for this operation here since it also provides ring construction with stereochemical control over up to four adjacent asymmetric centers. This choice virtually dictates the synthesis from the available starting material, piperonal, to the lactam acid **2**, in eight operations and 14% overall yield, as previously reported.[3] This intermediate possesses a rigid *trans*-decalin skeleton, assured by the cycloaddition, with a sterically dominant axial carboxyl for steric control of ring-C functionalization as well as for bridge formation to nitrogen. When the latter operation was carried out first, the crinine skeleton was formed,[3] but in the subsequent functionalization of ring C full steric control was not achieved.[4] This communication reports prior functionalization of ring C and the stereospecific conversion to haemanthidine (**1**) and tazettine, a closely related isomeric alkaloid.[1]



2

The less stable axial orientation of methoxyl at C-3 can reliably be created by the opening of the more hindered, 2,3-epoxide cis to the carboxyl in **2**. Such an epoxide was created by iodolactonization of **2** (KI_3 in $NaHCO_3$ solution) to **3**, Z = I, mp 270° (92%),



3

(1) W. C. Wildman in "The Alkaloids," Vol. VI, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1960.

(2) J. B. Hendrickson, manuscript in preparation.

(3) J. B. Hendrickson, C. Foote, and N. Yoshimura, *Chem. Commun.*, 9, 165 (1965); the overall yield has been improved since this report.

(4) Unpublished work by Dr. S. Grossert in these laboratories.