Qualitatively similar data were obtained for subtilisin[15] (the last two columns in Table I)[16] and porcine liver carboxyl esterase.[17] In the latter case, k_{cat}/K_M in the enzymatic hydrolysis of hydrophobic ethyl hydrocinnamate was nearly 8 times as high as for hydrophilic ethyl L-lactate. However, in octane, ethyl lactate's k_{cat}/K_M for the carboxyl esterase catalyzed transesterification with propanol was 47 times as high as for ethyl hydrocinnamate. Hence for all three enzymes a complete reversal of substrate specificity occurs upon replacement of water with octane as the reaction medium. The described phenomenon is expected to be general since water plays a critical role in all types of enzyme–substrate interactions and therefore its substitution should have a major impact on substrate specificity of enzymes.

Registry No. 1, 2361-96-8; *N*-Ac-L-His-OMe, 36097-48-0; *N*-Ac-L-Ser-OMe, 54322-41-7; $Me(CH_2)_6Me$, 111-65-9; ethyl hydrocinnamate, 2021-28-5; ethyl L-lactate, 687-47-8; α-chymotrypsin, 9004-07-3; subtulisin, 9014-01-1; carboxyl esterase, 9016-18-6.

(15) Protease from *Bacillus subtilis*, also known as subtilisin Carlsberg (EC 3.4.21.14) (for a review, see: Ottesen, M.; Svendsen, I. *Methods Enzymol.* **1970**, *19*, 199–215), was obtained from Sigma in a crystallized and lyophilized form with a specific activity of 9.6 casein units per mg of solid.

(16) The magnitude of the effect here is not as dramatic because the hydrophobic binding site in subtilisin is not as pronounced as in chymotrypsin (ref 3, Chapter 1).

(17) This enzyme (EC 3.1.1.1; for a review, see: Krisch, K. In *The Enzymes*, 3rd ed.; Boyer, P. D., Ed.; Academic Press: New York, 1971; Vol. 5, pp 43–69) was purchased from Sigma as a suspension in $(NH_4)_2SO_4$ with a specific activity of 200 ethyl butyrate units per mg of protein. Ammonium sulfate was removed by dialysis, and the esterase was lyophilized from aqueous phosphate buffer (pH 7.8). Basic conditions of the esterase reactions were the same as those employed for chymotrypsin and subtilisin.

(18) This work was financially sponsored by Miles Laboratories.

6-Methylenebicyclo[3.1.0]hex-3-en-2-yl Cation, an Isomer of Benzyl Cation

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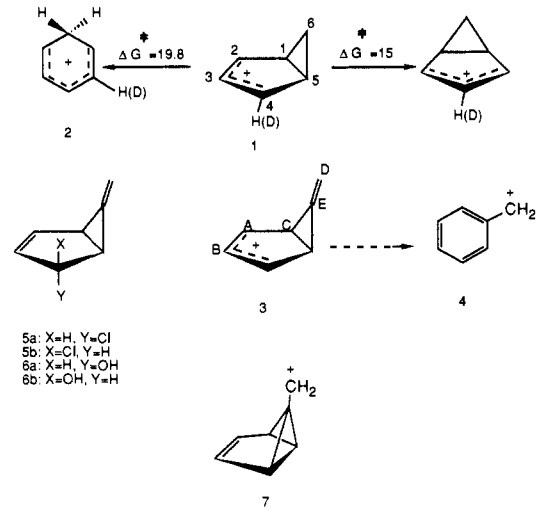
Previous work[1a] reported the preparation and proton NMR observation of the stable bicyclo[3.1.0]hex-3-en-2-yl cation (**1**). Cation **1** was shown by an isotopic labeling experiment to undergo a slow degenerate rearrangement at −90 °C ($\Delta G^{\ddagger}$ = 15 ±1 kcal/mol). At −20 °C, irreversible decomposition to unidentified products competes with ring opening to benzenonium ion (**2**) ($\Delta G^{\ddagger}$ = 19.8 kcal/mol).[1a-f]

Insertion of a methylene group at C_6 of **1** would give cation **3**, whose decyclization to benzyl cation **4** should be exothermic by ~63 kcal/mol (from bond additivities). We hoped that this driving force might facilitate the direct spectroscopic detection of benzyl cation (**4**), which hitherto has not been reported, in the literature, as a long-lived species.[1g]

A 10:1 mixture of chlorides **5a,b**, precursors of cation **3**, was best prepared by treatment of a mixture of epimeric 6-methylenebicyclo[3.1.0]hex-3-en-2-ols, **6a,b**[2] with $SOCl_2$ (4 equiv) and pyridine (1 equiv) in pentane solution at −15 °C. Purification of the chloride mixture was effected by bulb-to-bulb distillation at 0.2 torr followed by careful preparative gas chromatography (5% OV-101, column temperature 45 °C).[3]



Cation solutions were prepared by using the standard method,[4] by codistillation of **5a/5b** and SbF_5 under vacuum into a receiver at −196 °C, followed by addition of SO_2ClF to the distillate and warming to −110 °C. Cation **3**, so formed, shows the ^1H and ^{13}C NMR spectra shown in Figure 1 and interpreted[5] in Table I.

The NMR spectrum of the cation is unchanged below −110 °C. From −110 to −70 °C, the spectrum undergoes reproducible and reversible changes. The peak heights for protons of the five-membered ring (A, B, and C) decrease as the signals broaden into the base line. By −70 °C, these peaks completely disappear; however, recooling returns the peaks to their original heights. At temperatures above −70 °C, the *exo*-methylene signal D at δ 5.34 irreversibly disappears. Recooling once this signal has vanished produces no peaks. If the sample is recooled before the signal from proton D is completely gone, protons A, B, and C reappear in the same relative proportions but in overall diminished intensities (as compared to either tropylium tetrafluoroborate, added to the receiver prior to the preparation of **3**, or to the impurity peak at δ 9.07 presumably resulting from HF or HCl, generated within the sample). The ^{13}C NMR of the cation at −70 °C shows only signals corresponding to D and E. At temperatures above −70 °C cation **3** irreversibly decomposes to unidentified products (even in dilute solution), in contrast to cation **1** which is stable up to −20 °C. Thus far, photolysis of the sample at −150 °C for extended periods of time has led only to decomposition.

Magnetization transfer was observed among the five-membered ring protons A, B, and C. At −110 °C, saturation of proton A causes a decrease in intensity of both peaks B and C, saturation of proton B causes mainly a decrease in intensity of peak A, and saturation of proton C causes mainly a decrease in intensity of peak A. Saturation of proton D does not cause any peaks to decrease in intensity. These results suggest that the methylenecyclopropane ring of cation **3** rapidly migrates around the five-membered ring.

The changes in line width with temperature were used in conjunction with the KUBO[6] program to obtain rates of the ring-walk process over the temperature range of −110 to −70 °C. From −105 to −81 °C, the peak width of A increases from 8.9 to 61.3

(1) (a) Vogel, P.; Saunders, M.; Hasty, N. M., Jr.; Berson, J. A. *J. Am. Chem. Soc.* **1971**, *93*, 1551. See also: (b) Childs, R. F.; Winstein, S. *J. Am. Chem. Soc.* **1968**, *90*, 7146. (c) Koptyug, V. H.; Kuzubova, L. I.; Isaev, I. S.; Manatyuk, V. I. *Chem. Commun.* **1969**, 389. (d) Childs, R. F.; Sakai, M.; Winstein, S. *J. Am. Chem. Soc.* **1968**, *90*, 7144. (e) Childs, R. F.; Parrington, B.; *Chem. Commun.* **1970**, 1540. (f) Swatton, D. W.; Hart, H. *J. Am. Chem. Soc.* **1967**, *89*, 5075. (g) Olah, G. A.; Porter, R. D.; Jeuell, C. L.; White, A. M. *J. Am. Chem. Soc.* **1972**, *94*, 2044.

(2) Pikulin, S.; Berson, J. A. *J. Am. Chem. Soc.* **1985**, *107*, 8274.

(3) Characterized by ^1H and ^{13}C NMR spectroscopy. At temperatures above 55 °C, **5a/b** rearranges smoothly to benzyl chloride in solution (benzene or CH_3CN) or in the gas phase.

(4) Saunders, M.; Cox, D.; Lloyd, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 6656.

(5) (a) The alternative 6-methylenebicyclo[2.1.1]hex-2-enyl cation structure is unlikely on energetic grounds, being more strained than **3** by ~23 kcal/mol[5b] and lacking the resonance energy of an allylic cation (~15 kcal/mol). Moreover it does not account for the ^{13}C or ^1H NMR spectra which, by analogy to the 7-norbornenyl cation, should show a ^{13}C peak for C_2–C_3 near δ 125 and an ^1H resonance for H_2–H_3 near δ 7.5. (b) Greenberg, A.; Liebman, J. F., *Strained Organic Molecules*; Academic Press: New York, 1978; p 94. (c) Olah, G. A.; Liang, G. *J. Am. Chem. Soc.* **1975**, *97*, 6803 and references cited therein.

(6) (a) Saunders, M. *Tetrahedron Lett.* **1963**, 1699. (b) Saunders, M. In *Magnetic Resonance in Biological Systems*; Ehrenberg, A., Malmström, B. G., Vänngård, T., Eds.; Pergamon Press: Elmsford, NY, 1967; p 85.

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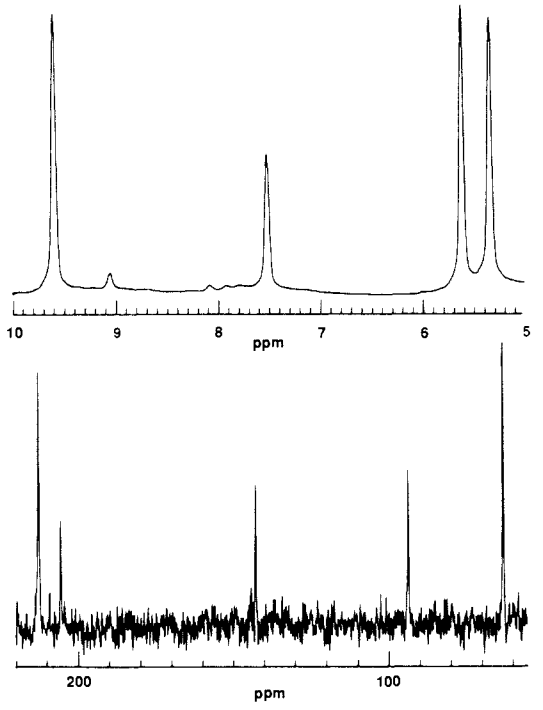

Figure 1. ^1H (upper) and ^{13}C NMR (lower) spectra of the 6-methylenebicyclo[3.1.0]hex-3-en-2-yl cation **3** at −110 °C.

Table I. NMR Spectral Assignments to the 6-Methylenebicyclo[3.1.0]hex-3-en-2-yl Cation (**3**)

	^1H NMR		^{13}C NMR	
position	rel intensity[d]	chem shift, δ[a,b]	mult[e,f]	chem shift, δ[a,c]
A	1.9	9.60	d	212.5
B	1.0	7.52	d	142.5
C	2.1	5.61	d	62.9
D	2.0	5.34	tr	93.4
E			s	205.4

[a] In ppm relative to Me_4Si. [b] Calibrated by setting the central peak of the methyl triplet of anhydrous ethanol to 1.11 ppm at 250 MHz at −110 °C. [c] Calibrated by setting the methyl peak of anhydrous ethanol to 17.2 ppm at 62.9 MHz at −110 °C. [d] Relative to signal from proton B set to unity. Estimated error ±10%. [e] $J_{C\text{-}H}$ could not be determined because of insufficient signal-to-noise ratio in the spectrum. [f] Proton and carbon with a given letter designation shown to be associated by off-resonance decoupling experiments.

Hz, the peak width of B increases from 10.4 to 40.2 Hz, and the peak width of C increases from 8.4 to 31.4 Hz. An Arrhenius plot of the data[7] shows an activation energy of 10.6 ± 0.2 kcal/mol and a value for log A of 14.3 ±0.2 (A in s^{-1}) for the circumambulation.[8] Based on these results, the KUBO program predicts that a rate of $\sim 10^4$ would be necessary to observe the onset of coalescence. Extrapolation from the line-width data yields a temperature of about −45 °C, which is above the temperature where decomposition occurs.

The chemical shifts for the A, B, and C protons of cation **3** match rather closely those of H_2 (δ 9.97), H_3 (δ 7.49), and H_1 (δ 5.27) of cation **1**. The circumambulatory sigmatropic rearrangement of the methylene-substituted cation **3**, however, is much faster than that of **1**: $k_3/k_1 = 2.2 \times 10^7$ at −110 °C. This difference must in some fashion be attributed to the terminal olefin, and it is tempting to speculate that it directly participates in the ring-walk process. For example, the rate enhancement might be associated with the dicyclopropylcarbinyl cationic character of species **7**, which could be an intermediate or transition state in the rearrangement of **3** but has no counterpart in the rearrangement of **1**.

From the fact that decomposition of **3** has a half-life of at least an hour at −70 °C, $\Delta G^{\ddagger}$ for ring-opening **3** → **4** may be estimated as at least 11.5 kcal/mol. It seems likely that this substantial barrier to realization of a highly exothermic reaction is associated with its orbital-symmetry-forbidden character.

Acknowledgment. R.M.J. acknowledges support by a fellowship administered by the American Chemical Society Division of Organic Chemistry and sponsored by the Proctor and Gamble Co. Partial support was also provided by National Science Foundation Grants CHE 8310857 and CHE 8506590.

(7) Peak A was chosen since it is least obscured by other signals in the spectrum and is located in a region free from rolls in the base line.

(8) The KUBO matrix used to represent the ring walk is available from the authors.

Intramolecular 2-Azaallyl Anion Cycloadditions. Application to the Synthesis of Fused Bicyclic Pyrrolidines

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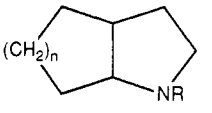
The widespread occurrence of the pyrrolidine ring in nitrogen-containing natural products makes synthetic methods for their assembly a high priority. Commonly, pyrrolidines are found fused to one or more additional rings, as in **1**.[2] In this paper, we report our initial successful investigations into the construction of such systems using the first examples of the intramolecular cycloaddition of 2-azaallyl anions (eq 1).[3]



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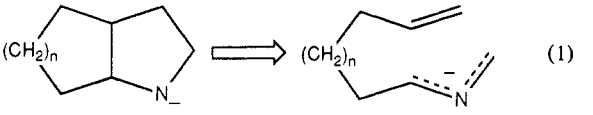

(1)

Although 2-azaallyl anions were first studied by Ingold in 1929,[4] Kauffmann pioneered their cycloadditions in the early 1970's, leading to a review of his work in 1974.[5] Successful cycloaddition was possible with a variety of anionophiles, such as activated olefins, allenes, and acetylenes. Despite the obvious potential,

(1) Recipient of a Dreyfus Foundation Grant for Newly Appointed Faculty in Chemistry, 1984–1989.

(2) For example, mesembrine,[a] lycorine,[b] erysotrine,[c] dendrobine,[d] scandine,[e] and sirodesmin A.[f] (a) For a recent synthesis and leading references, see: Meyers, A. I.; Hanreich, R.; Wanner, K. T. *J. Am. Chem. Soc.* **1985**, *107*, 7776. (b) Fuganti, C. In *The Alkaloids*; Manske, R. F. H., Holmes, H. L., Eds.; Academic Press: New York, 1975; Vol. XV, Chapter 3. (c) Hill, R. K. *Ibid.* **1967**; Vol. IX, Chapter 12. (d) For a recent synthesis, see: Roush, W. R. *J. Am. Chem. Soc.* **1980**, *102*, 1390. (e) Cordell, G. A. *Introduction to the Alkaloids. A Biogenetic Approach*; Wiley: New York, 1981; pp 758–760. (f) Curtis, P. J.; Greatbanks, D.; Hesp, B.; Cameron, A. F.; Freer, A. A. *J. Chem. Soc., Perkin Trans 1* **1977**, 180. For an approach to bicyclic pyrrolidines with the nitrogen at the bridgehead position, see: Pearson, W. H. *Tetrahedron Lett.* **1985**, *26*, 3547.

(3) Intramolecular azomethine ylide cycloadditions have recently been reported, leading to ring systems such as **1**. Our approach should be complementary. See: (a) Wang, C.-L. J.; Ripka, W. C.; Confalone, P. N. *Tetrahedron Lett.* **1984**, *25*, 4613. (c) Confalone, P. N.; Huie, E. M. *J. Am. Chem. Soc.* **1984**, *106*, 7175. (c) DeShong, P.; Kell, D. A.; Sidler, D. R. *J. Org. Chem.* **1985**, *50*, 2309. (d) Smith, R.; Livinghouse, T. *Tetrahdron* **1985**, *41*, 3559. (e) Armstrong, P.; Grigg, R.; Jordan, M. W.; Malone, J. F. *Ibid.* **1985**, *41*, 3547. (f) Wenkert, D.; Ferguson, S. B.; Porter, B.; Qvarnstrom, A.; McPhail, A. T. J. *Org. Chem.* **1985**, *50*, 4114.

(4) Ingold, C. K.; Shoppee, C. W. *J. Chem. Soc.* **1929**, 1199.

(5) Kauffmann, T. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 627.

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