product has been obtained from etioluciferamine (**2**) in two steps.[8-10]

Acknowledgments. This work was supported by a predoctoral fellowship from the National Institutes of Health to T. P. K. and by a grant from the Public Health Service (Research Grant No. 5R01 7868 from the National Institute of Neurological Diseases and Blindness).

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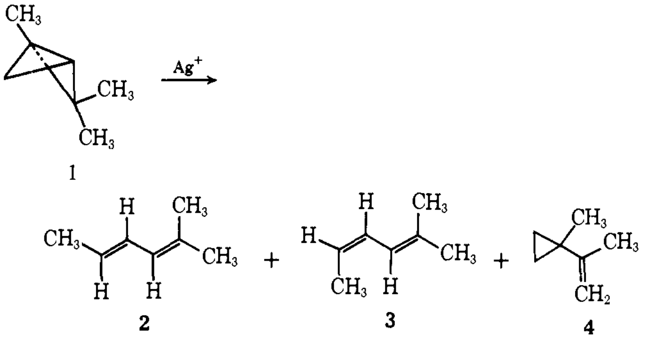
Silver(I) Ion Catalyzed Rearrangements of Strained σ Bonds. VII. Evidence for the Intervention of Argento Carbonium Ions in Bicyclo[1.1.0]butane Isomerizations[1]

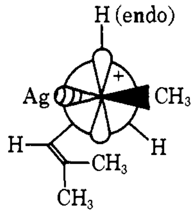
Sir:

A vexatious problem in the Ag$^+$-catalyzed rearrangement of bicyclo[1.1.0]butanes has been elucidation of the precise mechanism by which the highly stereoselective isomerization[2,3] to dienes occurs. Earlier, we presented kinetic data which demonstrated the establishment of a rapid preequilibrium with a 1:1 complex and subsequent rate-determining rearrangement of this species.[2] The skeletal reorganizations examined to the present time seemingly involved C_1C_2 and C_3C_4 bond rupture and the stereochemistry of the products hinted at the operation of symmetry-disallowed rotations about the remaining σ bonds. However, reservations can be expressed about the concertedness of these processes because of the improbability that a lone silver(I) ion can coordinate simultaneously in the appropriate manner with the two indicated bicyclobutane bonds. Furthermore, Ag$^+$ is certain to operate as an electrophilic species and bicyclobutanes are now recognized to interact with such entities by initial cleavage of the central (C_1C_3) bond.[4] We have now secured evidence showing that discrete intermediates intervene after complexation of bicyclobutanes to Ag$^+$; additionally, the selectivity observed in the generation of these intermediates and their chemical reactivity implicate them to be argento carbonium ions.

The behavior of 1,2,2-trimethylbicyclobutane (**1**)[5] is illustrative. Exposure of dilute CDCl$_3$ solutions of **1** to catalytic amounts of AgBF$_4$ (added at −70°, followed by warming to 40°) results in essentially quantitative isomerization to dienes **2**[6a] and **3**[6b] (90% yield, ratio 4.5:1), together with **4**[5] (8%) and four very minor products. This isomerization is most simply viewed as the result of C_1C_2 and C_1C_3 bond cleavage to afford the more highly substituted argento carbonium ion and hydrogen migration from either or both of two possible conformations (**5** and **6**).[7,11] The formation of the second double bond will in all likelihood be thermodynamically controlled, in agreement with the predominance of **2**.



1 **2** **3** **4**



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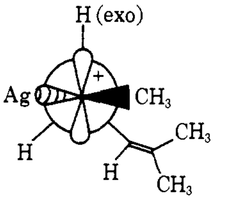

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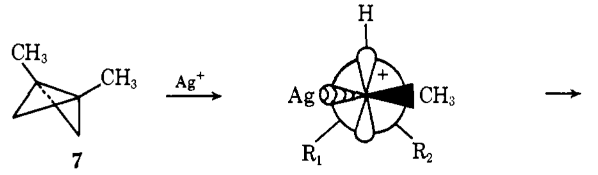
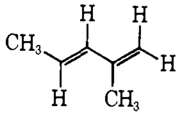
Similar treatment of **7**[12] (to 25% conversion[13]) gives rise to 2-methyl-*trans*-1,3-pentadiene (**9**).[14] In this instance, the rehybridization which occurs subsequent



7

8a, $R_1 = CH_2{=}C(CH_3){-}$; $R_2 = H$
b, $R_1 = H$; $R_2 = CH_2{=}C(CH_3){-}$



9

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[1] For paper VI of this series, see L. A. Paquette, R. S. Beckley, and T. McCreadie, *Tetrahedron Lett.*, in press.

[2] L. A. Paquette, S. E. Wilson, and R. P. Henzel, *J. Amer. Chem. Soc.*, **93**, 1288 (1971).

[3] L. A. Paquette, G. R. Allen, Jr., and R. P. Henzel, *ibid.*, **92**, 7002 (1970).

[4] L. A. Paquette, G. R. Allen, Jr., and M. J. Broadhurst, *ibid.*, in press, and references therein.

[5] L. Skattebol, *Tetrahedron Lett.*, 2361 (1970); W. R. Moore, K. G. Taylor, P. Muller, S. S. Hall, and Z. L. F. Geibel, *ibid.*, 2365 (1970).

[6] (a) The structure was established on the basis of its spin-decoupled 100-MHz nmr spectrum, catalytic hydrogenation to 2-methylhexane, and independent synthesis from *trans*-crotonaldehyde and isopropylidenetriphenylphosphorane. (b) The first two criteria in part a were utilized for structure proof of **3**.

[7] Existing theoretical calculations pertaining to hydrogen migration in ethylidene do not permit differentiation between rearrangement to the filled or unfilled orbital.[8] However, the recently established parallelism between migratory aptitudes to carbonium[9] and carbenoid[10] centers is most consistent with stereoelectronically controlled shifts to the unfilled orbital on the sp^2-hybridized carbon in the two systems. Accordingly, we assign analogous behavior to argento carbonium ions.

[8] R. Hoffmann, G. D. Zeiss, and G. W. Van Dine, *J. Amer. Chem. Soc.*, **90**, 1485 (1968); see also R. Hoffmann, R. Gleiter, and F. B. Mallory, *ibid.*, **92**, 1460 (1970).

[9] Y. E. Rhodes and T. Takino, *ibid.*, **92**, 5270 (1970), and references therein.

[10] A. R. Kraska, L. I. Cherney, C. G. Moseley, G. M. Kaufman, and H. Shechter, submitted for publication.

[11] The question of the relative reactivities of conformers **5** and **6** is potentially resolvable since exo and endo hydrogen migration should be specific for a given intermediate. This aspect of the problem is currently receiving attention.

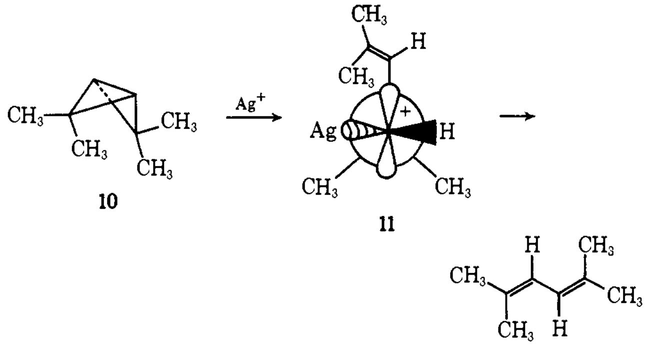
[12] W. von E. Doering and J. F. Coburn, Jr., *Tetrahedron Lett.*, 991 (1965); M. R. Rifi, *J. Amer. Chem. Soc.*, **89**, 4442 (1967); K. Griesbaum and P. E. Butler, *Angew. Chem., Int. Ed. Engl.*, **6**, 444 (1967).

[13] Longer reaction times were observed to lead gradually to a complex mixture which included a substantial amount of higher boiling products.

[14] Identical with authentic sample procured from Chemical Samples Co., Columbus, Ohio.

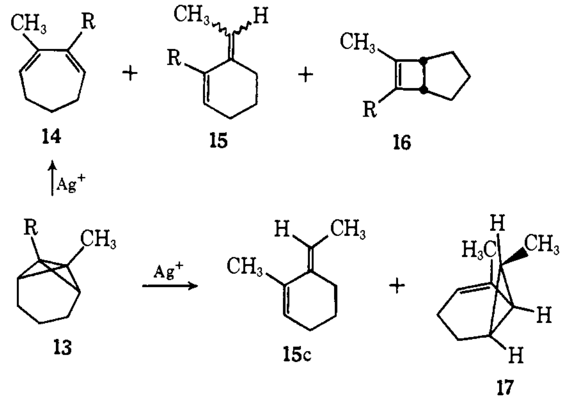
to hydrogen migration in **8a** and **8b** is seen to lead to trans olefin, presumably for steric reasons.

The essentially quantitative conversion of **10**[15] to **12**[16] under the previously stated conditions is also consistent with the intervention of argento carbonium ion **11**. In particular, the exclusivety of vinyl migration in **11** conforms to the greater migratory aptitude of vinyl (relative to alkyl) groups to cationic centers.[9]



10 **11** **12**

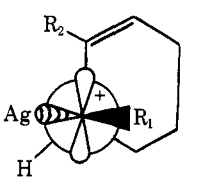
The influence of incremental alkyl substitution upon the course of bicyclobutane rearrangements is perhaps most strikingly manifested in the tricyclo[4.1.0.0^{2,7}]heptane series. Previously, the Ag$^+$ promoted isomerization of the parent hydrocarbon was shown to give rise quantitatively to *cis,cis*-1,3-cycloheptadiene.[2,3] In contrast, when **13a**[17] was heated with $AgClO_4$ (0.136 *M*) in anhydrous benzene at 40°, there was produced a mixture of four isomeric hydrocarbons **14a** [29%; $\delta_{TMS}^{CDCl_3}$ 5.72 (m, 3), 1.7–2.5 (m, 6), and 1.78 (t, $J = |1.5\ Hz|$, 3)], **15a** (29%, syn:anti 4:1),[18] and **16a** [42%; $\delta_{TMS}^{CDCl_3}$ 5.64 (m, 1), 2.88–3.17 (m, 2), 0.87–1.84 (m, 6), and 1.60 (methyl)]. The structure of **14a** follows from its nmr spectrum and its ready photoisomerization to **16a**. By rearranging **13b** in the same manner (50°), ultimate positioning in **14–16** of the second tricycloheptane bridgehead carbon was revealed by the absence in their nmr spectra of the indicated olefinic protons (b series). Isomerization of **13c**[17] as above was found to yield **15c**[19] (80%) and **17**[20] (20%).



14 **15** **16** **13** **15c** **17**

a, R = H; b, R = D; c, R = CH_3

These data can be interpreted to mean that the argento carbonium ion formed from tricyclo[4.1.0.0^{2,7}]heptane undergoes exclusive 1,2-vinyl shift by way of conformer **18a** ($R_1 = R_2 = H$) and subsequent 90° rotation to produce ring-expanded cis,cis-conjugated diene. In the case of **13a**, two additional factors require consideration. Conformer **18b** ($R_1 = CH_3$; $R_2 = H$) is more sterically congested and therefore less stable than **18a**; also the carbonium ion center is now more stable. Vinyl migration no longer dominates. Some hydrogen shift occurs from conformer **19b**, but the major product, **16**, stems from a more deep seated skeletal rearrangement. Dimethyl derivative **13c** exhibits a pronounced tendency for hydrogen shift, presumably as a result of the greater reactivity of conformation **19c** ($R_2 = R_2 = CH_3$) in this instance.



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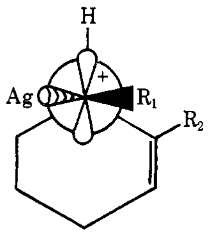

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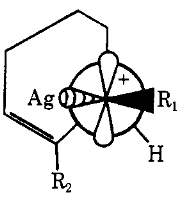

20

The argento carbonium ion hypothesis also satisfactorily explains the stereoselectivity encountered in the Ag$^+$-catalyzed rearrangements of *exo,exo*- and *endo,-exo*-2,4-dimethylbicyclobutanes.[2] The establishment of the present mechanism would mean, of course, that the observed stereochemical results reflect not orbital symmetry control in the bond reorganization, but rather a combination of steric, kinetic, and thermodynamic factors.

In summary, it is proposed that interaction of silver(I) ion with bicyclobutanes results in rupture of *two* strained bonds to produce, at least in certain cases, a cationic species with Ag$^+$ bonded to an sp^2-hybridized electron pair. The skeletal bond reorganizations of cubyl systems under similar conditions have recently been formulated as proceeding *via* metal insertion with initial rupture of *one* strained bond and carbonium ion rearrangement.[21] Whether or not the initial phases of these two mechanisms are related or distinctly different remains to be elucidated and is under active consideration. Clearly, the later stages of these two catalytic processes differ dra-

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(15) H. K. Hall, Jr., C. D. Smith, E. P. Blanchard, Jr., S. C. Cherkofsky, and J. B. Seija, *J. Amer. Chem. Soc.*, **93**, 121 (1971).

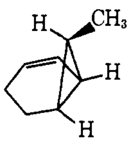
(16) An nmr spectrum of authentic **12** may be found in the Varian Spectra Catalog (no. 515).

(17) The preparation of these hydrocarbons has been described by G. L. Closs and L. E. Closs, *J. Amer. Chem. Soc.*, **85**, 2022 (1963).

(18) The ultraviolet and nmr spectra of **15a** were identical with those previously reported for these substances: P. D. Bartlett, *Quart Rev., Chem. Soc.*, **24**, 473 (1970). We thank Professor Bartlett for providing us with copies of the nmr spectra. The assignments in the paper by Bank, *et al.* (S. Bank, C. A. Rowe, A. Schriesheim, and L. A. Naslund, *J. Org. Chem.*, **33**, 221 (1968)), should be reversed.

(19) Independently synthesized by reaction of 2-methyl-2-cyclohexenone with ethylidenetriphenylphosphorane: $\delta_{TMS}^{CDCl_3}$ 5.02–5.74 (m, 2), 1.50–2.52 (m, 6), 1.80 (br s, 3), and 1.72 (d, $J = |7\ Hz|$, 3).

(20) $\delta_{TMS}^{CDCl_3}$ 5.0–5.24 (br, m, 1), 1.48–2.46 (br, m, 7), and 0.58–1.20 (br, 6). Structural assignment based on spectral comparisons with authentic i, ii (from 1,3-cyclohexadiene, ethylidene iodide, and diethylzinc), and iii (analogous treatment of 2-methyl-1,3-cyclohexadiene).



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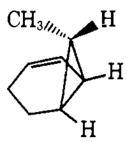
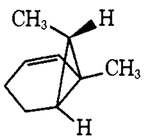


ii



iii

(21) L. Cassar, P. E. Eaton, and J. Halpern, *Chem. Commun.*, 40 (1971).

matically, the former leading to olefin production and the latter to bond relocation.[22] Studies in progress are intended to provide information underlying the causative factors behind this contrasting behavior.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for their partial support of this research. We also thank Professor H. Shechter for a most stimulating discussion.

[22] A review of Ag^+ catalysis will soon appear: L. A. Paquette, *Accounts Chem. Res.*, in press.

[23] (a) National Science Foundation Graduate Trainee, 1970–1971; (b) National Institutes of Health Postdoctoral Fellow, 1970–1971.

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Received February 19, 1971

The Use of Carbon-13 Nuclear Magnetic Resonance (Cmr) Spectroscopy in Biosynthetic Studies. Incorporation of Carboxyl and Methyl Carbon-13 Labeled Acetates into Cephalosporin C

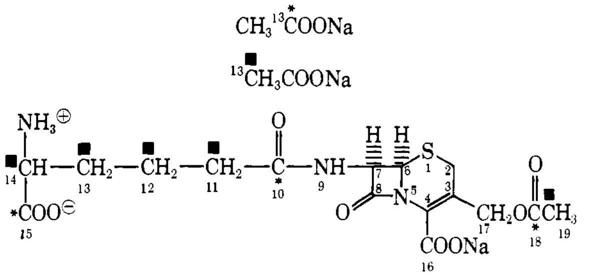
Sir:

The study of biosynthetic pathways leading to the formation of penicillins and cephalosporins has resulted in the understanding of the role of certain precursors involved in the formation of this class of microbial products.[1] Most of these studies have been conducted with the aid of radiotracer techniques. The availability of cmr spectroscopy prompted us to use this method in the study of incorporation of ^{13}C-labeled acetate into cephalosporin C. Cmr spectroscopy has been shown to be useful in the elucidation of biosynthetic pathways of microbial metabolites of a completely different type.[2,3]

Submerged cultures of *Cephalosporium acremonium*, a superior antibiotic producing mutant, M 8650-3,[4] were grown at 25° on a rotary shaker (250 rpm) in a complex medium.[5] In the first experiment, cephalosporin C was pulse labeled with *[1-^{13}C]*sodium acetate, and in the second with *[2-^{13}C]*sodium acetate[6] by the addition of aliquots of 1 ml of the aqueous solution[7] of the respective acetates to 70 ml of the broth in individual flasks after 46, 54, 66, 78, and 90 hr of incubation. Fermentation broth was collected by filtration after 115 hr. Cephalosporin C was purified and crystallized as the sodium salt.[8]

Chemical shifts of the 16 carbon atoms (Table I) in the natural abundance cmr spectrum of cephalosporin C–Na salt (I) were obtained from 25.2-MHz spectra using dioxane as internal reference. The assignment of the resonances was based on off-resonance and single-frequency proton decoupling experiments.[9] The carbon signals were divided into groups according to the number of directly bonded protons on the basis of the off-resonance spectra. Individual proton decoupling frequencies, obtained from the reported proton spectra of cephalosporin derivatives,[10] were then used to provide an unambiguous assignment of each of the carbons bearing protons. Thus, the assignment of C-2, C-6, C-7, C-11, and C-14 was uniquely defined by single frequency proton decoupling. Although C-12 and C-13 could not be differentiated from each other by this technique, their resonances were readily identified on the basis of chemical shifts and using appropriate models.[11]

Table I. Incorporation of ^{13}C-Labeled Acetates and Carbon-13 Chemical Shifts of Cephalosporin C (I)



Assignment[a]	Chemical shifts[b]	Rel intensities[c]		
		Normal abundance	$^{13}CH_3$-COO^-Na^+ labeled	$CH_3{}^{13}COO^-$-Na^+ labeled
C-2	167.8	1.0	1.0	1.0
C-3	58.5	1.0	1.2	1.0
C-4	74.5	1.2	1.2	1.2
C-6	135.2	1.0	0.8	0.8
C-7	133.2	1.0	1.0	1.0
C-8	24.3	1.0	1.0	1.4
C-10	12.0	1.0	1.2	2.2
C-11	158.1	1.0	2.0	1.0
C-12	172.6	1.0	1.8	1.2
C-13	163.1	1.0	1.8	1.2
C-14	137.9	1.0	4.6	1.0
C-15	14.1	1.0	1.0	5.0
C-16	20.6	0.8	0.8	1.0
C-17	127.8	1.0	1.0	0.8
C-18	14.6	1.0	1.0	3.6
C-19	173.2	0.8	3.6	0.8

[a] This numbering system is different from the accepted numbering system for this class of compounds and is used uniquely for an easy identification of chemical shifts. [b] Spectra were recorded at 25.2 MHz on the Varian XL-100-15 using 12-mm tubes and the signal from a concentric tube containing acetone-d_6 as lock. All chemical shifts and intensities were obtained from *ca.* 1 *M* aqueous solutions containing $\sim$10% dioxane as internal reference. Shifts are given in parts per million relative to CS_2 and have uncertainties of about ±0.1 ppm. [c] These are measured relative intensities from the spectra run under essentially identical instrumental conditions and accurate to ±0.2. The signal from acetone-d_6 provided a convenient check on relative intensities between samples. In order to obtain per cent incorporation, the figures in columns 4 and 5 should be corrected according to the formula $\%\ \text{incorp} = (100/62)\cdot(I - 1)$, where I is the observed intensity.

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[1] E. P. Abraham and G. G. F. Newton in "Antibiotics," D. Gottlieb and P. D. Shaw, Ed., Vol. II, Springer Verlag, New York, N. Y., 1967, pp 1–16.

[2] M. Tanabe, H. Seto, and L. F. Johnson, *J. Amer. Chem. Soc.*, **92**, 2157 (1970).

[3] M. Tanabe, T. Hamasaki, H. Seto, and L. F. Johnson, *Chem. Commun.*, 1539 (1970).

[4] D. W. Dennen and D. D. Carver, *Can. J. Microbiol.*, **15**, 175 (1969).

[5] Experimental details pertaining to condition of fermentation will be published elsewhere.

[6] *[1-^{13}C]*- and *[2-^{13}C]*sodium acetate, Merck Sharp & Dohme, Canada, 62–63 atom % ^{13}C.

[7] The solution was prepared by dissolving 20 mg of acetate in 1 ml of water and sterilizing by membrane filtration.

[8] P. W. Trown, E. P. Abraham, G. G. F. Newton, C. W. Hale, and G. A. Miller, *Biochem. J.*, **84**, 157 (1962).

[9] (a) M. Tanabe, T. Hamasaki, D. Thomas, and L. F. Johnson, *J. Amer. Chem. Soc.*, **93**, 273 (1971); (b) J. D. Roberts, F. J. Weigert, J. I. Kroschwitz, and H. J. Reich, *ibid.*, **92**, 1338 (1970).

[10] R. D. G. Cooper, P. V. Demarco, C. F. Murphy, and L. A. Spangle, *J. Chem. Soc. C*, 340 (1970).

[11] A. Allerhand, D. W. Cochran, and D. Doddrell, *Proc. Nat. Acad. Sci. U. S.*, **67**, 1093 (1970).