were applied to strips of Whatman 3MM paper and were developed as descending chromatograms with 2-propanol–concentrated ammonia–water (6:3:1, by volume). The radiochromatograms from the 0.1-mL experiments are shown in Figure 2. The chromatograms from the 0.4-mL incubations were used for the quantitation of ^{14}C in each chromatographic peak[12] and for the elution of selected fractions for further identification. In the presence of **1** in the incubations there was a gross accumulation of a product with an R_f value of 0.17 corresponding to **2**. When this substance was eluted from the papers and rechromatographed, it cochromatographed with authentic **2**, and after hydrolysis with alkaline phosphatase it gave mevalonate in 95% yield. Quantitatively, **2** accounted for 40.4% of the total ^{14}C added to the incubations containing **1** compared with 3.4% in the uninhibited reaction mixtures after 10-min incubations. In addition, there was a decrease in the amount of IPP (5.3% compared with 10.0% of the total ^{14}C in the absence of **1**) presumably owing to the decreased availability of 5-diphosphomevalonate.

The observations taken together can only mean that **1** is a specific inhibitor of 5-phosphomevalonate kinase. We examined the possibility that **1** might also be a substrate for phosphomevalonate kinase. However, incubation of S_{10} preparations with **1** and [γ-^{32}P]ATP gave no evidence of the phosphorylation of **1** to a phospho[^{32}P]phosphate.

The mechanism of inhibition of phosphomevalonate kinase by **1** is unknown at present since we have studied its effects so far only in the multienzyme system of rat liver S_{10} preparations and—in a quantitative way—only at one concentration of mevalonate. Although there is no information about the properties of phosphomevalonate kinase of rat liver, it is worth noting that the K_m value of (*R*)-5-phosphomevalonate for the partially purified enzyme from pig liver was found to be ~300 μM.[13] The inhibition of phosphomevalonate kinase by a racemic mixture of **1** with an apparent K_i ($I_{50}^{CO_2}$) of 145 μM is the more surprising as no substrate inhibition of the pig-liver enzyme could be detected even at a concentration of 1.5 mM of (*R*)-5-phosphomevalonate.[13]

Acknowledgments. This work was supported by grants from the National Institutes of Health (HL-12745 to G.P. and GM21400 to R.E.) and from the American Heart Association Greater Los Angeles Affiliate (Investigative Group Award 521IG2 to G.P.) and the PSC-BHE Faculty Research Award Program of CUNY and the Merck Sharp and Dohme Research Laboratories (to R.E.). We thank Mr. Geoffrey Boehm and Mrs. Aniko Meenan for their excellent technical help.

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(12) ^{14}C compounds can be measured on portions of dried chromatograms with the best efficiency (60 to 65%) by curling up the cut out portions of the paper strips into a roll of ~1-cm diameter and inserting them into the scintillation vials containing 10 mL of RPI 3a70B scintillation fluid. Counting of ^{14}C was done in a Packard Tri-Carb scintillation spectrometer, Model No. 3320.
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(14) Research Fellow of the American Heart Association Greater Los Angeles Affiliate while this research was carried out.

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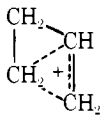
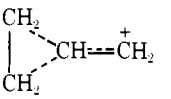
Low-Temperature Carbon-13 Nuclear Magnetic Resonance Spectroscopic Investigation of $C_4H_7^+$. Evidence for an Equilibrium Involving the Nonclassical Bicyclobutonium Ion and the Bisected Cyclopropylcarbinyl Cation[1]

Sir:

Much experimental and theoretical work has been directed toward elucidating the nature of the cationic intermediate(s) involved in cyclopropylcarbinyl, cyclobutyl, and allylcarbinyl interconversions under so-called "stable-ion" as well as solvolytic conditions.[2,3] Whereas all experimental evidence on $C_4H_7^+$ indicates that the species is a nonclassical cation,[2-4] controversy continues regarding the equilibrium geometry of this cation, with some favoring the bicyclobutonium structure **1a**, and others the "bisected" cyclopropylcarbinyl arrangement (**1b**).[2-4] We now report that an investigation of $C_4H_7^+$ under



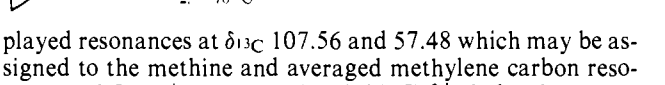
1a



1b

"stable-ion" conditions at low temperatures by ^{13}C NMR spectroscopy indicates the coexistence of at least two structural isomers of $C_4H_7^+$ in rapid equilibrium with one another.

An SbF_5-SO_2ClF-SO_2F_2 solution of $C_4H_7^+$ was prepared according to previously described techniques[3] at ca. −125 °C, employing cyclopropylcarbinol-*1*-^{13}C (43% ^{13}C).[5-7] The 20-MHz ^{13}C NMR spectrum of this solution at −70 °C dis-



played resonances at $\delta_{^{13}C}$ 107.56 and 57.48 which may be assigned to the methine and averaged methylene carbon resonances of $C_4H_7^+$, respectively (Table I).[3d] Under these conditions, the carbon-13 label is distributed nearly randomly between the methylene and methine positions of $C_4H_7^+$, indicating that hydride migrations between methine and methylene centers are occurring at rates which are slow on the NMR time scale.[8]

The ^{13}C NMR chemical shifts obtained on varying the temperature of this SbF_5-SO_2ClF-SO_2F_2 solution of $C_4H_7^+$ between −61 and −132 °C are given in Table I.[9] It is apparent that decreasing temperatures cause substantial movement of the methine and average methylene carbon resonances (downfield and upfield, respectively). The temperature de-

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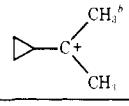
Table I. ^{13}C NMR Shieldings of $C_4H_7^+$ and the 1-Methylcyclopropylcarbinyl Cation at Various Temperatures[a]

species	temp, °C	$\delta_{^{13}CH}$	$\delta_{^{13}CH_2}$	$\delta_{^{13}C^+}$	$\delta_{^{13}CH_3}$
$C_4H_7^{+b}$	−61	106.78	58.95		
	−70[c]	107.56	57.48		
	−76	107.64	57.22		
	−80	108.02	56.55		
	−88	108.52	55.58		
	−99	109.20	54.33		
	−101	109.38	53.97		
	−107	109.73	53.46		
	−112	110.03	53.02		
	−115	110.25	52.63		
	−127	111.00	51.36		
	−132	111.32	50.89		
	−62	66.49	58.52	249.63	31.52
	−130	65.86	59.11	251.49	31.67

[a] All spectra were obtained on a Varian Associates FT-80 NMR spectrometer. The chemical shifts were measured from the CF_2ClH resonance of an external (capillary) $CF_2ClH/(CD_3)_2O$ reference and converted to parts per million relative to external $(CH_3)_4Si$ utilizing $\delta_{^{13}C}$ (external $(CH_3)_4Si$) = $\delta_{^{13}C}$ (CF_2ClH) + 116.60. [b] In SbF_5-SO_2ClF-SO_2F_2 solution. [c] Excluded from data analysis.

Table II. Comparison of ^{13}C NMR Chemical Shifts of $C_4H_7^+$ with Those Anticipated for Several Possible Structural Isomers

structure	$\delta_{^{13}CH}$	av $\delta_{^{13}CH_2}$
$C_4H_7^+$ (this work)	115 ± 3	47 ± 3
1a[a]	114	56
1b[a]	76	116
	319	

[a] Anticipated ^{13}C NMR shieldings of possible structural isomers taken from ref 3d and converted to parts per million relative to external (capillary) $(CH_3)_4Si$ utilizing $\delta_{^{13}C}$ (external $(CH_3)_4Si$) = $-\delta_{^{13}C}$ (CS_2) + 193.7.

pendences over a similar temperature range of the methine, methylene, and methyl carbon resonances of the 1-methylcyclopropylcarbinyl cation[3b,d,10] in the same solvent system were also studied and are given in Table I.[11] The latter experiments show that the temperature dependences of the shifts of a "static" cation are not of sufficient magnitude to account for the rather large temperature-induced shifts observed for $C_4H_7^+$.[12] The data thus suggest an equilibrium between two or more energetically similar structural isomers of $C_4H_7^+$ which interconvert rapidly on the NMR time scale, even at 63.1 MHz and −155 °C.[13]

Assuming that only two species are involved in the equilibrium, the ^{13}C NMR shifts of each set of exchanging sites were calculated from optimization of a linear least-squares fit of the observed chemical shifts vs. the populations of the lower energy isomer of $C_4H_7^+$ with respect to the ^{13}C NMR shifts of the exchanging sites as well as the enthalpy and entropy differences between the two isomers.[14]

These calculations indicate that the ^{13}C NMR shifts of the methine and average methylene carbons of the lower energy isomer of $C_4H_7^+$ are $\delta_{^{13}C}$ 115 ± 3 and 47 ± 3, respectively.[14,15] Comparison of these calculated ^{13}C NMR shieldings with those anticipated for **1a** and **1b** and the cyclobutyl cation[4] (Table II) show that they are only consistent with the formulation of the most stable isomer of $C_4H_7^+$ as the bicyclobutonium ion (**1a**).[16] The experimental uncertainties[14,15] in the input parameters δ and T preclude any quantitative assessment of the ^{13}C NMR shifts which can be attributed to the higher energy isomer of $C_4H_7^+$.[14] However, the observation that the methine and average methylene carbon resonances of the higher energy isomer of $C_4H_7^+$ must be shifted upfield and downfield, respectively, relative to the corresponding resonances in the more stable isomer, suggests that the bisected cyclopropylcarbinyl cation structure (**1b**) might reasonably be assigned to the higher energy species (Table II).[3d]

Although the experimental uncertainties[14,15] in the input parameters δ and T also prevent calculation of the enthalpy (ΔH) and entropy (ΔS) differences between the structural isomers of $C_4H_7^+$, we conclude that the nonclassical bicyclobutonium ion (**1a**) and the bisected cyclopropylcarbinyl cation (**1b**) are rather similar energetically. Indeed if ΔS for the equilibrium is assumed to be 0, the free-energy difference is 1000 ± 500 cal. Thus the results of this investigation are in general accord with those of our previous studies[3b,d,17] and serve to reinforce the contention [3b,d,17] that the preference demonstrated for a bisected cyclopropylcarbinyl cation geometry in suitably substituted systems in no way precludes, or represents a discontinuum from, the adoption of the bicyclobutonium ion geometry by $C_4H_7^+$ as has been suggested in the recent literature.[2c]

Acknowledgment. We thank Professor F. A. L. Anet of the University of California at Los Angeles for the generous use of his facilities to obtain the 63.1-MHz ^{13}C NMR spectra.

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(4) Various geometries for **1a** and **1b** are discussed in ref 2 and 3. See also Howden, M. E. H.; Roberts, J. D. *Tetrahedron.* **1963**, *19*, 403–414.
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(7) This solution was made up from 0.067 g of cyclopropylcarbinol-*1*-^{13}C (43% ^{13}C), 1.0 g of SbF_5, 1 mL of SO_2ClF, and 1 mL of SO_2F_2.
(8) Staral, J. S.; Roberts, J. D. *J. Am. Chem Soc.* following paper in this issue.
(9) Below −140 °C, the ^{13}C NMR spectrum of $C_4H_7^+$ in this solvent system was severely viscosity broadened, whereas above −60 °C, $C_4H_7^+$ rapidly decomposes to unidentified products.
(10) Saunders, M.; Rosenfield, J. *J. Am. Chem. Soc.* **1970**, *92*, 2548–2549.
(11) Prepared from 0.081 g of 1-methylcyclopropylcarbinol, 1.0 g of SbF_5, 1 mL of SO_2ClF, and 1 mL of SO_2F_2.
(12) In principle, some of the temperature dependence of the carbon shieldings of $C_4H_7^+$ might arise from differences in zero-point energy associated with having the ^{13}C at different CH_2's in the labeled $C_4H_7^+$ cation, but this effect is likely to be far less than the observed changes.

(13) The temperature dependences of the ^{13}C NMR shifts attributable to an equilibrium process suggest the possibility of concomitant temperature dependences for the $^{1}J_{^{13}CH}$ couplings. The $^{1}J_{^{13}CH}$ values of the methine and methylene resonances in this system were measured at intervals from −76 to −132 °C but no systematic temperature dependences were observed. The broadness of the resonances lines ($\nu_{1/2}$ ~12 Hz, probably because of long-range carbon–proton couplings) precluded detection of small changes in these couplings. Nonetheless, the low- and high-field methylene proton resonances[3d] of $C_4H_7^+$ at 60 MHz shifted upfield by 0.06 and 0.12 ppm, respectively (relative to external $CF_2ClH/(CH_3)_4Si$), between about −85 to −115 °C. The ^1H NMR resonance of the methine proton of $C_4H_7^+$ was too broad to permit accurate measurement of its temperature dependence. The methylene proton shifts of the O-protonated cyclobutanol present in these solutions (see ref 8) remained essentially constant over this temperature range.
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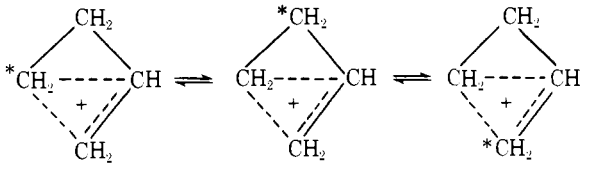
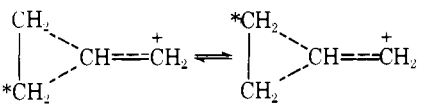
Observation by Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Hydride Shifts in $C_4H_7^+$ Derived from Cyclopropylcarbinol-*1*-^{13}C in SbF_5–SO_2ClF–SO_2F_2 Solution[1]

Sir:

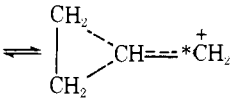
The interconversion in carbocationic reactions of cyclobutyl, cyclopropylcarbinyl, and allylcarbinyl derivatives has been the subject of many investigations since its discovery in 1950.[2,3] Although controversy continues to surround the precise nature



1a **1b** **1c**



2a **2b**



2c

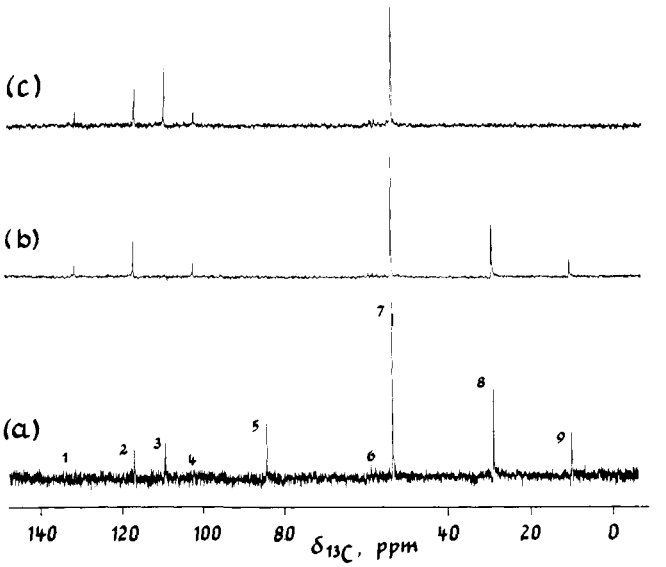
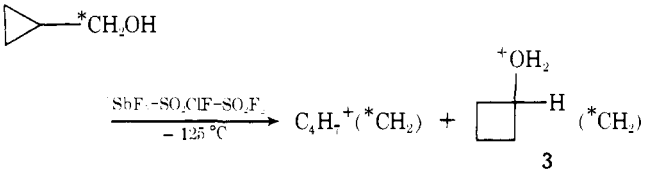


Figure 1. Fourier transform, 20-MHz ^{13}C NMR spectra (at −100 °C of SbF_5–SO_2ClF–SO_2F_2 solutions): (a) $C_4H_7^+$ and O-protonated cyclobutanol **3** from cyclopropylcarbinol; (b) $C_4H_7^+$ and O-protonated cyclobutanol **3** from cyclopropylcarbinol-*1*-^{13}C (43% enrichment); (c) $C_4H_7^+$ after warming the solution described in (b) to −70 °C for 20 min and cooling to −100 °C. The resonance lines are assigned as follows: 1, 2, 4 = CF_2ClH of external $CF_2ClH/(CD_3)_2O$ used as reference and field-frequency lock signal; 3, 7 = CH and average CH_2, respectively, of $C_4H_7^+$; 5, 8, 9 = C-1, C-2 + C-4, and C-3, respectively, of **3**; 6 = $(CD_3)_2O$ of external reference.

of the "nonclassical" $C_4H_7^+$ cationic intermediate(s) involved in these transformations, the very rapid equilibration of the methylene carbons is well established. At present, opinion is divided as to whether the equilibration process involves rapidly interconverting bicyclobutonium ions (**1a–c**) or "bisected" cyclopropylcarbinyl cations (**2a–c**).[2,3] In contrast, no evidence has been reported to indicate that hydride migrations occur in these intermediates.[2-6] We now report that the ^{13}C NMR spectrum of an isotopically labeled $C_4H_7^+$ under stable-ion conditions provides unequivocal evidence for slow occurrence of such hydride shifts.

An SbF_5–SO_2ClF–SO_2F_2 solution of $C_4H_7^+$ was prepared according to previously described techniques at about −125 °C, employing cyclopropylcarbinol-*1*-^{13}C (43% ^{13}C).[4h,7-9] A second SbF_5–SO_2ClF–SO_2F_2 solution of $C_4H_7^+$ was prepared



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for comparison purposes from nonisotopically enriched cyclopropylcarbinol under the same conditions.[10] The FT 20-MHz ^{13}C NMR spectra of these solutions at −100 °C are shown in Figure 1.[11] These ^{13}C NMR spectra display resonances of an additional, previously unreported,[2,3,4h] species with $\delta_{^{13}C}$ 84.2 (d, 167), 29.2 (t, 143), and 10.1 (t, 149) as well as the resonances of the methine and *averaged* methylene carbons of the $C_4H_7^+$ cation at $\delta_{^{13}C}$ 109.1 (d, 182) and 53.6 (t, 179), respectively.[2,3,4h,11] The 60-MHz ^1H NMR spectrum of this new species in SbF_5–SO_2ClF–SO_2F_2 at −100 °C consists of a doublet (J = 3 Hz, 2 H) at δ 8.78, a broad multiplet centered at 5.6 (1 H), and two broad, partially coincidental multiplets centered at 2.8 (4 H) and 2.1 (2 H). Comparison of these ^1H and ^{13}C NMR parameters with those reported for cyclobutanol[12] and O-protonated alcohols[13] shows that this substance is O-protonated cyclobutanol (**3**), a wholly reason-

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