eq 3, to give the observed product. In a variant of the pinacol-pinacolone rearrangement, KO-*t*-Bu in HO-*t*-Bu converts the hydroxymesylate **3b** back to the propellane ketone **1**, isolable in good yield.

Observations of this sort suggest that if tricyclo[4.2.2.$0^{1,5}$]decanes functionalized like **3** could be obtained from nonpropellane precursors, we might develop a new approach to propellane synthesis. Indeed, we have done this successfully. Titanium(0) intramolecular reductive coupling[10] of spirodione **5** at high dilution gives diol **3a** (25%, nonoptimized).[11] Reaction of **3a** with mesyl chloride/triethylamine in CH_2Cl_2 forms only monomesylate **3b**. This with base (conveniently lithium aluminum hydride in ether) goes cleanly to [4.2.2]propellane alcohol **7a**. As spirodione **5** is fairly readily available by standard aldol reactions, etc. (40% overall from cyclopentanone),[13] this synthesis provides for the first time a "photochemistry-free" approach to highly strained propellanes. This should prove very useful, particularly for the preparation of more complexly substituted propellanes.

Acknowledgment. The research efforts of The Principal Investigator are supported generously by the National Science Foundation (CHE-78-07430) and the National Cancer Institute of the National Institutes of Health (CA-12961). The high-field NMR instruments used were funded in part by the NSF Chemical Instrumentation Program and NCI via the University of Chicago Cancer Research Center (CA-14599). We thank G. H. Temme III for his contributions to the exploratory work.

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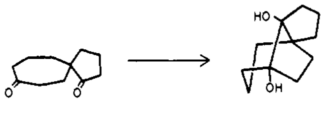
(10) McMurry, J. F.; Fleming, M. P.; Kees, K. L.; Krepski, L. R. *J. Org. Chem.* **1978**, *43*, 3255, and references therein.

(11) We have found that expansion of **5** with ethyl diazoacetate gives, after standard manipulation, spiro[4.6]undecane-1,8-dione (i) which on reduction with Ti(0) gives tricyclo[4.3.2.$0^{1,5}$]undecane-5,6-diol (ii), the carbon skeleton of the tumor inhibitor quadrone.[12]



i ii

(12) Ranieri, R. L.; Calton, G. J. *Tetrahedron Lett.* **1978**, 499.

(13) By modification of the procedures in ref 4.

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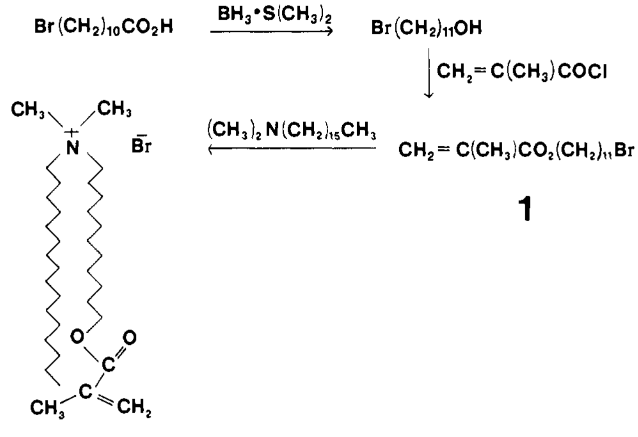
Polymerized Vesicles[1]

Sir:

In this communication, we introduce the concept of polymerized vesicles and report the synthesis of the first representative example.

Vesicles derived from naturally occurring phospholipids (liposomes) and synthetic surfactants are now being extensively investigated as carriers of drugs, models for biological membranes, and devices for photochemical solar energy conversion.[2-10] Because vesicles are thermodynamically unstable, however, all applications based on their long-term use are limited.[11] If vesicles could be prepared in polymerized forms, they should not only retain many of the key elements found in nonpolymerized analogues but should also be intrinsically more stable. In terms of drug delivery, they might serve as unique polydisperse, time-release carriers which, like liposomes, (1) promote the passage of drugs across cell membranes, (2) increase the plasma lifetime of the drug, (3) improve targeting prospects, and (4) retard drug catabolism.[4] They should, however, be less prone to in vivo (1) lipid-exchange processes, (2) direct removal and net transfer of lipids from vesicles, (3) uncontrolled leakage of entrapped drugs, and (4) vesicle–vesicle and vesicle–cell fusion.[12] Additionally, if polymerized vesicles promote the separation of charged photoproducts, they would be attractive candidates for practical solar energy devices.[7,9] We have been keenly interested in the concept of polymerized vesicles for these reasons and also because of the intriguing structural properties that these polymers would possess. In the following report, we present preliminary results which demonstrate the viability of our concept by showing that an ammonium surfactant can be polymerized in vesicle form and that the resulting vesicles *retain their spherical nature and aqueous interior while exhibiting enhanced stability.*

Scheme I



2

Ammonium salt **2** was synthesized by using the sequence of reactions shown in Scheme I.[13,14] Multilamellar vesicles were prepared by stirring 0.044 g (0.074 mmol) of **2** in 5 mL of D_2O at 58 °C for 10 min. Subsequent sonication (Branson LS-75, 75 W, 10 min, 58 °C, microtip probe) produced a clear stable solution, indicating the formation of small bilayer vesicles.[7] The Fourier transform ^1H NMR spectrum, while somewhat broadened, clearly showed the presence of the intact vinyl group (Figure 1A).

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(1) Supported by the National Science Foundation (Grant CHE-77-28366).

(2) Bangham, A. D. *Prog. Biophys. Mol. Biol.* **1968**, *18*, 29. Bangham, A. D.; Hill, M. W.; Hill, N. G. *Methods Membr. Biol.* **1974**, *11*, 38.

(3) Papahadjopoulos, D. *Ann. N. Y. Acad. Sci.* **1978**, *308*, 1.

(4) Juliano, R. L. *Can. J. Physiol. Pharmacol.* **1978**, *56*, 683.

(5) Kunitake, T.; Okahata, Y. *J. Am. Chem. Soc.* **1977**, *99*, 3860.

(6) Tran, C. D.; Klahn, P. L.; Romero, A.; Fendler, J. H. *J. Am. Chem. Soc.* **1978**, *100*, 1622.

(7) Fendler, J. H. *Acc. Chem. Res.* **1980**, *13*, 7.

(8) Mangel, M. *Biochim. Biophys. Acta* **1976**, *430*, 459. Toyoshima, Y.; Morino, M.; Sukigara, M. *Nature (London)* **1977**, *265*, 187. Stillwell, W.; Tien, H. T. *Biochim. Biophys. Acta* **1978**, *81*, 212. Ford, W. E.; Otvos, J. W.; Calvin, M. *Nature (London)* **1978**, *274*, 507; *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 3590.

(9) Infelta, P. P.; Gratzel, M.; Fendler, J. H. *J. Am. Chem. Soc.* **1980**, *102*, 1479. Nomura, T.; Escabi-Perez, J. R.; Sunamoto, J.; Fendler, J. H. *J. Am. Chem. Soc.* **1980**, *102*, 1484.

(10) Weinstein, J. N.; Magin, R. L.; Yatvin, M. B.; Zaharko, D. S. *Science (Washington, D.C.)* **1979**, *204*, 188.

(11) On prolonged standing, vesicles undergo fussion.[7]

(12) For an excellent review of vesicle–cell interactions, see: Poste, G.; Papahadjopoulos, D., ref 3, p 164.

(13) Procedures used for reduction of the carboxylic acid were identical with those previously described: Lane, C. F. *Aldrichimica Acta* **1975**, *8*, 20.

(14) **1**: ^1H NMR ($CDCl_3$) δ 6.08 (m, 1 H, vinyl), 5.50 (m, 1 H, vinyl), 4.13 (t, 2 H, $-OCH_2CH_2$), 3.39 (t, 2 H, CH_2Br), 1.94 (m, 3 H, $CH_3C{=}$), 2.0–1.1 (br m, 18 H, CH_2); anal. ($C_{15}H_{27}BrO$) C, H. **2**: ^1H NMR ($CDCl_3$) δ 6.08 (m, 1 H, vinyl), 5.52 (m, 1 H, vinyl), 4.15 (t, 2 H, $-OCH_2CH_2$), 3.65 (br m, 4 H $CH_2{}^+N$), 3.42 (s, 6 H, $CH_3{}^+N$), 1.95 (m, 3 H, $CH_3C{=}$), 2.0–1.1 (br m, 46 H, CH_2), 0.9 (m, 3 H, CH_3); anal. ($C_{33}H_{66}NO_2Br\cdot{}^1/_2H_2O$) C, H.

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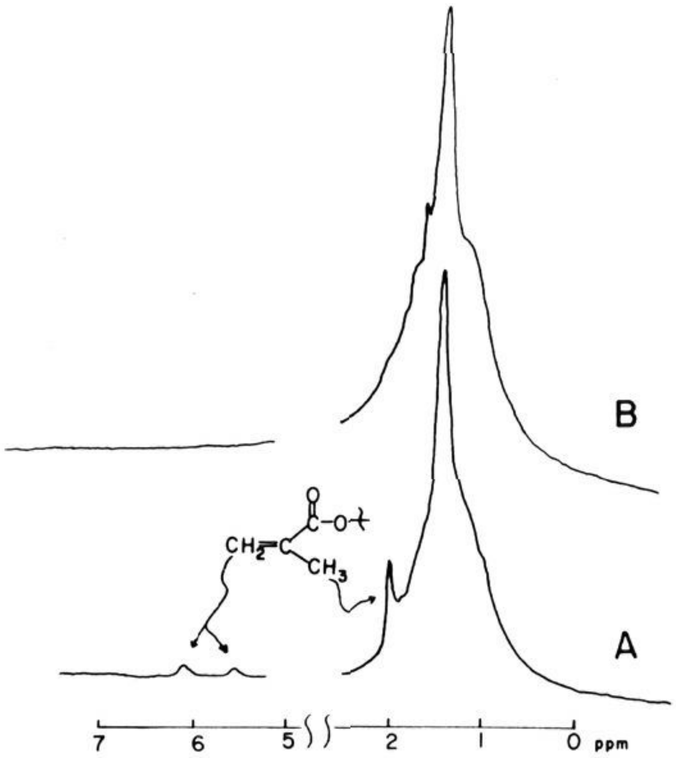

Figure 1. Fourier tranform ^{1}H NMR spectra of nonpolymerized (A) and polymerized (B) vesicles derived from **2** recorded in D_2O at 45 °C relative to external sodium 3-(trimethylsilyl)propionate (1000 scans), with a JEOL FX 60Q instrument.

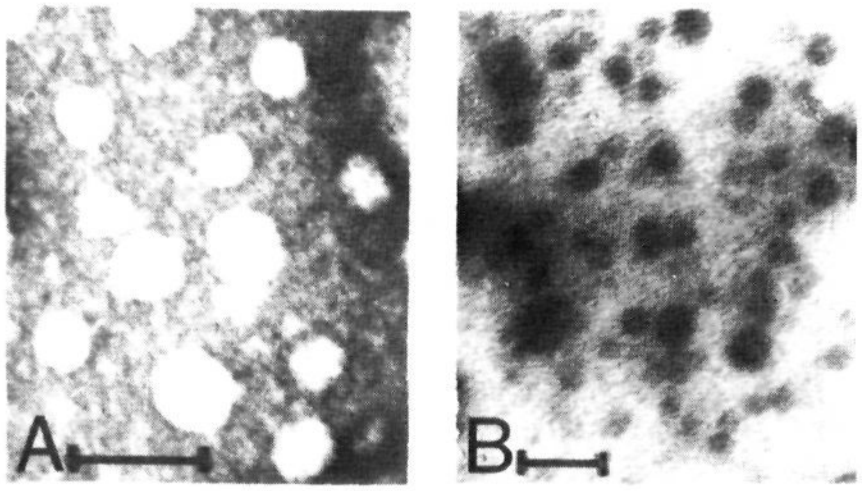

Figure 2. Electron micrographs of polymerized vesicles derived from **2** prepared by sonication in the absence (A) and presence (B) of uranyl acetate. Bar represents 1000 Å.

Addition of a free-radical initiator, AIBN (0.6 mg, 5 mol %), followed by brief sonication (75 W, 2 min, 58 °C) and heating (6 h, 80 °C) yielded a solution which remained clear on cooling to room temperature. Examination of the ^{1}H NMR spectrum revealed the complete disappearance of the vinyl and allyl protons. This fact, plus the additional line broadening observed, shows that polymerization has taken place (Figure 1B). An electron micrograph of this sample recorded on an RCA EMU-4A microscope confirmed the presence of closed spherical vesicles having diameters ranging between 200 and 700 Å (Figure 2A).[15] Similar vesicles, which were prepared by using an aqueous uranyl acetate solution (2%) instead of pure D_2O, are shown in Figure 2B.

Further evidence for closed vesicles comes from the entrapment of [^{14}C]sucrose. Thus, after sonic disspersal of **2** in water containing 20 μCi of [^{14}C]sucrose, and after polymerization, nonentrapped sucrose was removed by gel filtration on Sephadex G-50 with a Tris·NaCl buffer solution as the eluant.[16-18] Vesicles recovered from the void volume of the column indicated that approximately 0.02% of the sucrose became entrapped; analogous nonpolymerized vesicles derived from **2** (an identical concentration of surfactant was used) entrapped 0.04% of the sucrose.[19]

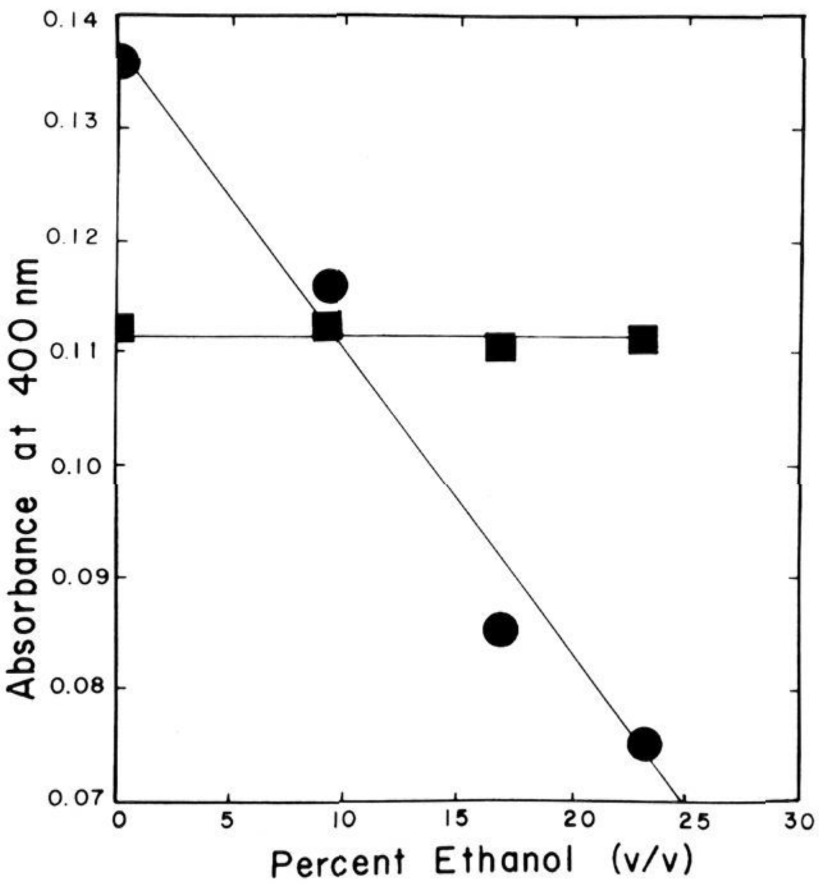

Figure 3. Plot of absorbance at 400 nm as a function of percent ethanol (v/v) for polymerized (■) and nonpolymerized (●) vesicles of **2**.

In order to evaluate the stability of these polymerized vesicles, we have examined their response to the addition of ethanol.[21] Experimentally, an aqueous solution of the vesicles was diluted with ethanol, and the observed absorbance was measured and corrected for the volume change.[22] Within experimental error, the turbidity (absorbance at 400 nm) was constant from 0 to 25% ethanol (v/v). In sharp contrast, similar experiments conducted with nonpolymerized vesicles derived from **2** showed a dramatic decrease in turbidity (Figure 3). These results clearly demonstrate that polymerization increases stability.

Detailed characterization of these and related vesicles is now under intensive investigation. Of immediate interest are (1) the determination of the degree of polymerization and the extent of inner, outer, and inner–outer "stitching" of the bilayers and (2) the control of stability and permeability properties through variation in the polymerization conditions and the addition of a cross-linking agent.[23] Efforts are also being made to prepare and characterize analogous phosphatidylcholine vesicles for possible use as drug carriers.

Acknowledgment. We are grateful to Drs. Noritaka Ohtani, Koushi Fukunishi, and Kenneth Siegesmund (Medical College

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(15) The sample for electron microscopy was prepared by mixing equal volumes of the polymerized vesicle solution with 2% aqueous uranyl acetate. One drop of the resulting solution was applied to a carbon-coated copper grid, and the grid was dried in a desiccator.

(16) Polymerization conditions were similar to those described in the text; the specific activity of sucrose was 360 μCi/μmol (obtained as a 20% ethanol solution from ICN Laboratories).

(17) Typically, 100 μL of the vesicle sample was chromatographed on 2.0 g of Sephadex G-50-150 (Sigma Chemical Co.)

(18) Tris·NaCl buffer solution (5 mM Tris-HCl + 0.1 M NaCl, pH 7.4).

(19) Preliminary permeability data obtained from dialysis experiments with seamless cellulose bags at 25 °C indicate that both polymerized and nonpolymerized vesicles derived from **2** exhibit apparent leakage rates of ~65%, which corresponds to the diffusion rate of nonentrapped sucrose out of the bag itself.[20] Because the leakage is so rapid, we have not yet been able to determine leakage rates out of the vesicles themselves

(20) The leakage rate is the amount of [^{14}C]sucrose diffusing through the vesicles and the bag into the dialysate per hour and is expressed as the percentage of the total [^{14}C]sucrose present inside of the bag at the beginning of the time period. Entrapment is expressed as the percent of entrapped sucrose relative to the 20 μCi initially present.

(21) Synthetic surfactant vesicles, like liposomes, are lysed when alcohol is added.[6]

(22) Corrected absorbance = observed absorbance × (volume of aqueous vesicle solution + volume of ethanol added)/volume of aqueous vesicle solution.

(23) The term cross-linking agent used here refers to a lipid monomer bearing two polymerizable groups, and differs from that used by Khorana in describing photoinitiated intermolecular coupling of one lipid with one other membrane component: Erni, B.; Khorana, H. G. *J. Am. Chem. Soc.* **1980**, *102*, 3888.

of Wisconsin) for providing valuable technical assistance and to K.S. for the generous use of his electron microscope laboratory. We are also grateful to Professors Robert MacDonald (Northwestern University), Rudy Juliano (University of Texas Medical School, Houston), and Janos Fendler (Texas A&M University) for valuable discussions.

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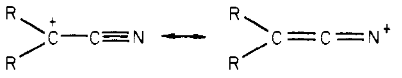
Received March 24, 1980

Significant Mesomeric Nitrenium Ion Character of the Cyanodiphenylmethyl Cation, the First Long-Lived Cyanocarbenium Ion[1]

Sir:

Nitrenium ions containing divalent positive nitrogen have been postulated as intermediates in rearrangement, synthesis, and cleavage of nitrogen-containing organic compounds.[2,3] Evidence for their existence as distinct species under stable ion conditions has been negative so far.[4] Attempted generation of nitrenium ions by protonating nitrosobenzenes resulted only in iminium-benzenium dications.[4,5] In principle, a cyano-substituted carbocation (**1a**) in its mesomeric form represents a nitrenium ion



1a 1b

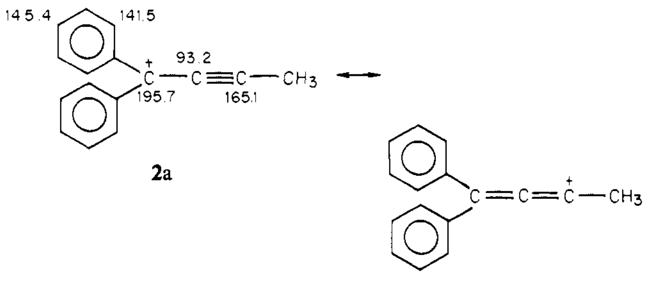
(**1b**), and this aspect has been considered recently in the solvolytic studies of α-cyano tosylates by Gassman and Talley.[6] The solvolytic study[6] of 1-cyano-1-octyl tosylate and 7-cyano-7-norbornadienyl tosylate indicated that the extent of mesomeric nitrenium ion character in the ions depended on the nature of the additional substituents on the cationic center.

We report now the preparation and ^1H, ^{13}C, and ^{15}N NMR spectroscopic observation of the cyanodiphenylmethyl cation **1**-C_6H_5 in FSO_3H/SO_2ClF solution. Careful addition of a solution of benzophenone cyanohydrin[7] in SO_2ClF to a tenfold excess of FSO_3H in SO_2ClF at -78°C resulted in a deep orange solution. The ^1H NMR spectrum of the solution showed an aromatic multiplet at γ 7.6–8.6 which is significantly deshielded over that in the neutral precursor (≈1 ppm; see Table I). In the ^{13}C NMR spectrum, the cationic carbon absorption was observed at δ 168.8 followed by a para carbon signal at δ 153.3. The cyano carbon absorbed at δ 112.1, about 9 ppm shielded over that in the neutral precursor. The substantial deshielding of both ortho and para carbons and the significant shielding of the cyano carbon are indicative of extensive charge delocalization into the aromatic ring as well as into the cyano group through the mesomeric nitrenium ion form. The cation **1**-C_6H_5 is comparable to the related 1,1-diphenyl-2-butynyl cation **2**[8] (which also has significant mesomeric vinyl cation contribution) although the charge delocalization into the aromatic ring is considerably less in the latter.

Table I. ^1H, ^{13}C, and ^{15}N NMR Data of Cyanodiphenylcarbenium Ion 1-C_6H_5 and Its Progenitor Benzophenone Cyanohydrin

substrate	^1H, δ^a	^{13}C, δ^a	^{15}N, δ^b
1-C_6H_5^{c}	7.6–8.6 (m)	C_{α}^{+} = 168.8, C_p = 153.3, C_o, C_o' = 148.2, 143.8, C_m = 133.7, -C≡N = 112.1	283.0
cyanohydrin^d	7–7.6 (m, 10 H, aromatic), 6.8 (s, 1 H, OH)	C_i = 142.5, C_o, C_p = 128.7, C_m = 125.9, -C≡N = 125.9, C_{α} = 75.1	253.0

[a] ^1H and ^{13}C NMR chemical shifts are in ppm from external capillary tetramethylsilane. [b] ^{15}N NMR chemical shifts are in ppm from external anhydrous ammonia. [c] In FSO_3H/SO_2ClF solution at -90 °C. [d] In $CDCl_3$ solution at 37 °C.



2a

2b

To ascertain the extent of mesomeric nitrenium ion character in **1**-C_6H_5, we prepared the 10% ^{15}N-enriched ion from the ^{15}N-enriched cyanohydrin precursor.[9] In the ^{15}N NMR spectrum, the cyano nitrogen was observed as a singlet (with no proton coupling) at δ 283.0, which is 30 ppm deshielded over that in the neutral precursor (δ 253.0). The lack of any proton coupling with the nitrogen clearly supports the formation of cyanodiphenylmethyl cation **1**-C_6H_5 and rules out any additional protonation on nitrogen. In fact, a substantial ^{15}N shielding is observed for nitrilium ions ($RC{\equiv}NH^+$) over the neutral nitrile precursor[10] (ca. 100 ppm). The observed 30-ppm deshielding clearly indicates carbon–nitrogen double-bond character. In fact, the ^{15}N chemical shift is more comparable to that of an imine (around δ 318).[10] The observed ^{15}N chemical shift data clearly support substantial mesomeric nitrenium ion contribution to the overall structure of the cation **1**-C_6H_5, in spite of competitive aryl ring delocalization.

Attempts to prepare analogous 1-cyano-1-cyclopentyl, 9-cyano-9-fluorenyl, 1-cyano-1-phenethyl, and 2-cyano-2-norbornyl cations from their corresponding cyanohydrins[7] under a variety of superacidic conditions were, however, unsuccessful. They indicated the formation of respective protonated carbonyl compounds along with a complex mixture of byproducts. We are continuing our studies of the elusive nitrenium ions under stable ion conditions.

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(1) Stable Carbocations. 232. For part 231 see: Olah, G. A.; Berrier, A. L.; Arvanaghi, M.; Prakash, G. K. S. *J. Am. Chem. Soc.*, submitted for publication.

(2) Gassman, P. G. *Acc. Chem. Res.* **1970**, *3*, 26–33.

(3) Gassman, P. G.; Hartman, G. D. *J. Am. Chem. Soc.* **1973**, *95*, 449–454.

(4) Olah, G. A.; Donovan, D. J. *J. Org. Chem.* **1978**, *43*, 1743–1750.

(5) (a) Okamoto, T.; Shudo, K.; Ohta, T. *J. Am. Chem. Soc.* **1975**, *97*, 7184–7185. (b) Ohta, T.; Shudo, K.; Okamoto, T. *Tetrahedron Lett.* **1977**, 101–104. (c) Shudo, K.; Ohta, T.; Endo, Y.; Okamoto, T. *Ibid.* **1977**, 105–108.

(6) Gassman, P. G.; Talley, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 1214–1216.

(7) Gassman, P. G.; Talley, J. J. *Tetrahedron Lett.* **1978**, 3773–3776.

(8) (a) Olah, G. A.; Spear, R. J.; Westerman, P. W.; Denis J-M. *J. Am. Chem. Soc.* **1974**, *96*, 5855–5859. (b) Prakash, G. K. S. Ph.D. Dissertation, University of Southern California, 1978.

(9) The 10% ^{15}N-enriched cyanohydrin was prepared from 10% ^{15}N-enriched trimethylsilyl cyanide which in turn was synthesized from enriched silver cyanide and trimethylsilyl chloride. The enriched silver cyanide was obtained by reacting aqueous silver nitrate solution with aqueous enriched sodium cyanide.

(10) Levy, G. C.; Lichter, R. L. "Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy", Wiley-Interscience: New York, 1979; p 67.

0002-7863/80/1502-6640$01.00/0