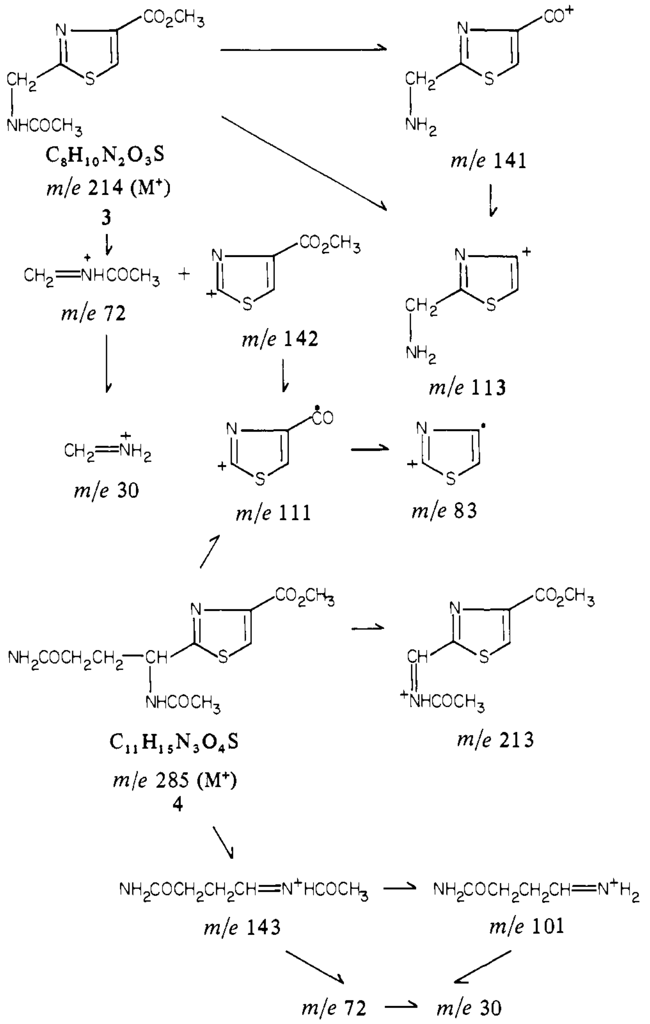
Scheme I. EI fragmentation of N-Ac-(gly)Thz-OMe and N-Ac-(gln)Thz-OMe



spectral analysis were unsuccessful, it was found possible to proceed in a quite workable manner by using the intact molecule. Detailed analysis of the dolastatin 3 electron-impact high-resolution mass spectrum led to the observations and assignments summarized in Table I. All of the evidence obtained from dolastatin 3 by chemical and spectroscopic techniques as well as biosynthetic considerations led to *cyclo*[Pro-Leu-Val-(gln)Thz-(gly)Thz] as the structure (**1**)[12] of this new P388 cell growth inhibitor.

Isolation[13] of the potentially important dolastatins in larger quantities combined with investigations directed at structural determinations and biological evaluations (U.S. National Cancer Institute) are currently in progress. Now it appears very likely that some of the dolastatins (such as **1**) will become readily available by total syntheses.

Acknowledgment. For very necessary financial assistance we are pleased to acknowledge support provided by Contract N01-CM-97297 with the Division of Cancer Treatment, NCI, National Institutes of Health, DHW, Grants CA16049-01–CA16049-07 awarded by the National Cancer Institute, DHW, Mary Dell Pritzlaff, the Olin Foundation (Spencer T. and Ann W.), the Fannie E. Rippel Foundation and the National Science Foundation Regional Facility at the University of South Carolina (CH78-18723). For other assistance we are also pleased to thank Drs. M. I. Suffness, J. M. Schmidt, J. A. Hasler, P. Lohavanijaya, J. A. McCloskey, D. Smith, J. R. Cronin, A. M. Yates, R. R. Inners, and J. Witschel, Jr.

Registry No. **1**, 80387-90-2; **2a**, 25438-22-6; **2b**, 80387-91-3; **3**, 80387-92-4; **4**, 80387-93-5.

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[12] Presumably, each amino acid unit bears the usual L configuration. But the resistance of dolastatin 3 to enzymatic cleavage suggests that the absolute configuration of each amino acid needs to be definitely established by chiral chromatographic or other methods. Eventually this point and the reverse order of bonding possibility (less likely by biosynthetic precedent) *Cyclo*[Val-Leu-Pro-(gly)Thz-(gln)Thz] can be resolved by the increased availability of dolastatin 3 for degradation and/or by total synthesis. The latter approach is quite feasible and a synthesis of (gly)Thz (**2a**) has already been described: Cross, D. F. W.; Kenner, G. W.; Sheppard, R. C.; Stehr, C. E. *J. Chem. Soc.* **1963**, 2143-2150.

[13] The sensitivity exhibited by some of the dolastatins suggests it is the presence of dehydroamino acid and/or thiazoline units that complicate purification procedures.

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^{13}C NMR Spectra of Carbonium Ions in the Solid State: The 2-Norbornyl Cation

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Studies of the structure and dynamics of the norbornyl cation are legion, but the interpretation of collected data remains a subject of controversy.[1] We report here studies of the norbornyl cation in the solid state over the 77–200 K range using cross-polarization magic-angle spinning (CPMAS) ^{13}C NMR spectroscopy.[2] The results will not resolve contentious issues, but they do provide important additional information that serves to bound speculation. Further, these results illustrate the potential power of MAS ^{13}C NMR spectroscopy to probe dynamic and structural characteristics of reactive intermediates. Results include (1) failure to find evidence for a "classical" norbornyl cation at 77 K, (2) the first solid-state NMR line-shape analysis of a chemical exchange process, the 6,1,2-hydride shift of the norbornyl cation.

exo-Norbornyl-^{13}C chloride, enriched at C-1, C-2, and C-6, was prepared by the route and in yields shown in Scheme I.[3] The 2-norbornyl-^{13}C acetate formed by buffered acetolysis (70 °C) of 2-(4-cyclopentenyl)ethyl-*1*-^{13}C *p*-nitrobenzenesulfonate (0.05 M) gave the ^{13}C distribution pattern shown in Scheme I.[4] Treatment of the acetate with Lucas reagent at 25 °C gave norbornyl-^{13}C chloride with additional scrambling of label at the indicated three carbons, but there was no detectable migration of label into other positions.[5]

An intimate solid mixture of the labeled norbornyl chloride and SbF_5 was prepared by vapor-phase codeposition.[6] Initial spectra of the solid codeposit at 190 K indicated only partial conversion to the cation. After 4 days at dry ice temperature, conversion was complete, and the label appeared to be statistically scrambled.

^{13}C spectra of the solid sample of the norbornyl cation at various temperatures were obtained with the use of cross-polarization,

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(1) (a) Olah, G. A. *Acc. Chem. Res.* **1976**, *9*, 41. (b) Brown, H. C.; von R. Schleyer, P. "The Non-Classical Ion Problem"; Plenum Press: New York, 1977.

(2) Schaefer, J.; Stejskal, E. O. Top. Carbon-13 NMR Spectrosc. **1979**, *3*, 281.

(3) The method of synthesis follows from work reported by (a) Lawton, R. G. *J. Am. Chem. Soc.* **1961**, *83*, 2300. (b) Hooz, J.; Gilianni, S. S. H *Can. J. Chem.* **1968**, *46*, 86. (c) Schmid, G. H.; Wolkoff, A. W. *J. Org. Chem.* **1967**, *32*, 239. (d) Murdock, K. C.; Angier, R. B. *Ibid.* **1962**, *27*, 2359.

(4) This result may be compared with related ^{14}C studies of: Lee, C. C.; Hahn, B. J. *J. Am. Chem. Soc.* **1969**, *91*, 6420.

(5) ^{13}C distributions were obtained from integrations of liquid-state spectra.

(6) Myhre, P. C.; Yannoni, C. S. *J. Am. Chem. Soc.* **1981**, *103*, 230.

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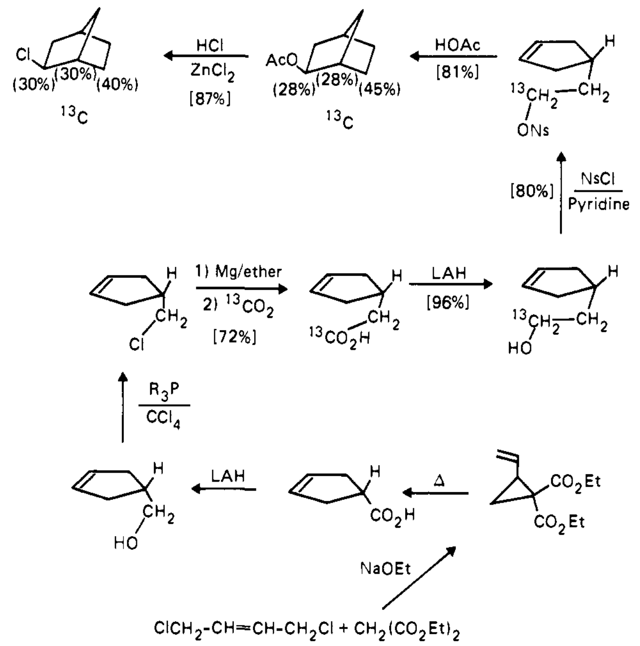
Scheme I. Norbornyl-^{13}C Chloride Synthesis



^{1}H, and ^{19}F decoupling and magic-angle spinning. A set of these spectra are shown in Figure 1 together with spectrometer parameters.[7] The spectrum at 200 K matches the reported solution-state spectrum at that temperature.[8] As the temperature is lowered, the downfield signal at 92 ppm broadens, and new signals develop at 124 and 21 ppm, reflecting slowdown of the 6,1,2-hydride shift. Attendant changes are observed for other carbon resonances (C-3,5,7). Peak positions then remain unchanged from about 130 to 77 K.[9]

A full line-shape analysis[10] of these spectra yielded exchange rates that were slower by a factor of 3–4 than those reported by Olah at equivalent temperatures.[11,12] The E_A value obtained, 6.1 ± 0.5 kcal mol^{-1}, does, however, agree with Olah's liquid state value, 5.9 ± 0.2 kcal mol^{-1}.

Dramatic solid-state effects on the rates of degenerate rearrangements have been observed in other systems.[6,14] The rather modest rate effects noted in this study and the close correspondence of solid- and liquid-state activation barriers for the 6,1,2-hydride shift suggest that entropy plays an important role in the exchange process in the solid state. It now seems obligatory to evaluate the rates and barrier of the 6,1,2-hydride shift in the crystalline (rather than amorphous) state and reevaluate the rates and barrier in the liquid state so that the nature and expected magnitudes of solid-state effects on rates can be more precisely understood.

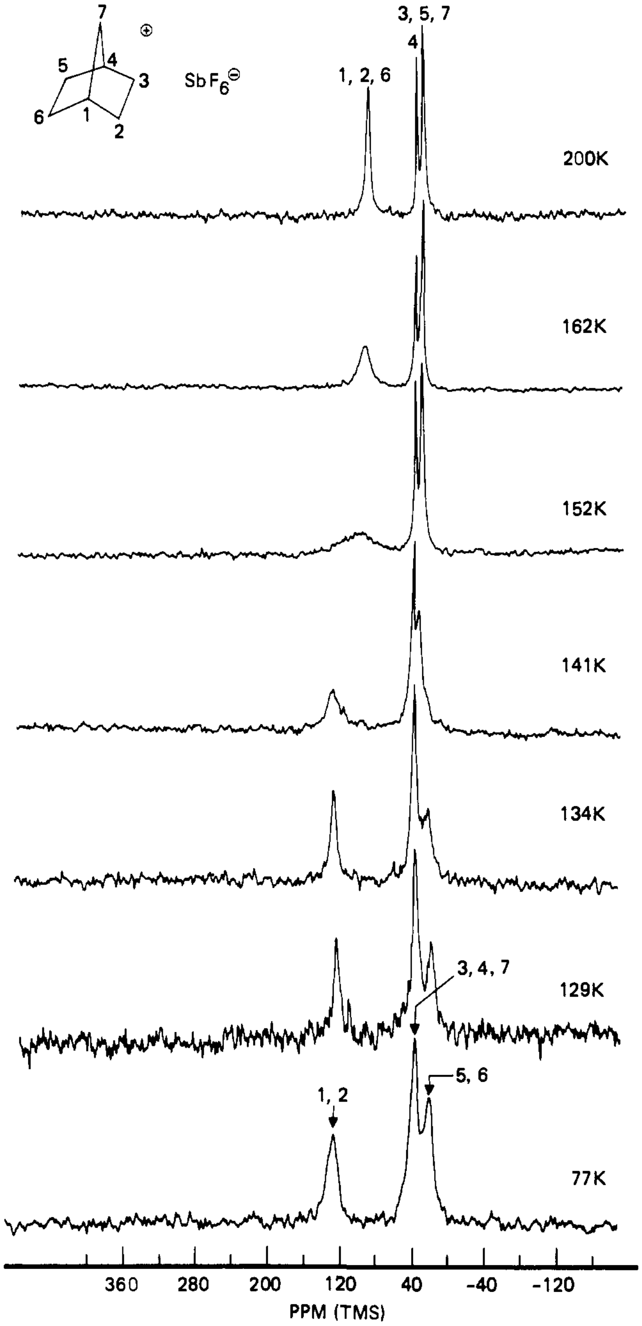


Figure 1. ^{13}C CPMAS solid-state NMR spectra of the 2-norbornyl cation. Cross polarization was achieved with 35-kHz matching of ^{1}H and ^{13}C rf fields, 1–5 ms contact time, and 1- or 2-s delay between scans. Decoupling field strengths during acquisition time were 18 mT (77 kHz) and 15 mT (60 kHz) for ^{1}H and ^{19}F, respectively. Temperature in K (ca. number of scans in thousands): 200 (2.5), 162 (3.0), 152 (3), 141 (7), 134 (23), 129 (37), 77 (2.3).

Uniform broadening of all resonances is observed as the temperature is lowered from 129 to 77 K and can arise from a variety of sources.[6] The important point is that the 1,2 peak does not

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[7] The linewidths shown in the spectra of Figure 1 are considerably smaller than those initially observed for the *sec*-butyl cation,[6] presumably because stronger ^{19}F decoupling has been used. Nonetheless, the ^{13}C resonances of crystalline carbonium ions (see: Fyfe, C. A.; Bruck, D.; Lyerla, J. R.; Yannoni, C. S. *J. Am. Chem. Soc.* **1979**, *101*, 4470) are narrower than those reported for carbonium ions prepared by codeposition and annealing.

[8] Olah, G. A.; Mateescu, G. D.; Riemenshneider, J. L. *J. Am. Chem. Soc.* **1973**, *95*, 8698.

[9] The low-temperature spectra do not match the corresponding liquid-state spectrum reported in ref 8, but they do appear to match the spectrum reported by Saunders.[15] The structural assignments shown in Figure 1 are based on liquid-phase spectra obtained by M. J. Goldstein and J. P. Dinnocenzo at 75.4 MHz. They differ from those reported by Olah,[8] as well as from those reported by Saunders.[15]

[10] Saunders, M. In "Magnetic Resonance in Biological Systems"; Ehrenberg, A., Ed.; Pergamon Press: Oxford, 1967; p 85. We thank Professor Saunders for making his NMR dynamics program available.

[11] Olah, G. A.; White, A. M.; Demember, J. R.; Commeyras, A.; Lui, C. Y. *J. Am. Chem. Soc.* **1969**, *92*, 4627. A line-shape analysis of chemical exchange in solids would be complicated if additional broadening arises when the exchange rate is comparable to the sample spinning rate (Suwelack, D.; Rothwell, W. P.; Waugh, J. S. *J. Chem. Phys.* **1980**, *73*, 2559); we saw no evidence for this kind of broadening.

[12] Temperatures were routinely monitored with a thermocouple positioned adjacent to the rotor in the exiting helium (spinning and cooling gas[13]) stream. These measurements were calibrated against temperatures measured in an empty spinning rotor positioned in the probe. We are aware that the temperature of a lossy sample such as cations in strongly acidic solid solution can be raised by rf heating from the decoupling fields; however, this was minimized by using a low rf duty cycle (2% maximum). The disparity we report here between exchange rates in the liquid and solid would even be greater if the sample temperature were higher than we have measured.

[13] Fyfe, C. A.; Mossbrugger, H.; Yannoni, C. S. *J. Magn. Reson.* **1979**, *36*, 61.

[14] Miller, R. D.; Yannoni, C. S. *J. Am. Chem. Soc.* **1980**, *102*, 7396.

appear to be significantly broader than the other resonances. Thus, the low-temperature spectra (Figure 1) give no evidence of freezing out of a "classical" norbornyl cation. This means only that if one views the spectra in terms of rapidly equilibrating classical ions, the barrier of that equilibration must be lower than about 3 kcal mol^{-1}. Within this limitation, one can adopt a different view. The recent studies of the appropriately deuterium labeled norbornyl cation by Saunders show very small isotopic splittings owing to perturbation of symmetry.[15] This result is stronger support, albeit less direct, for the "nonclassical" symmetrical norbornyl cation. We anticipate that we shall be able to conduct MAS ^{13}C NMR spectroscopy in the 30 K range in the future and look forward to additional studies of this and other cations over this extended temperature range.

Acknowledgment. We thank the National Science Foundation for financial support (Industry/University Cooperative Program, Grant CHE-8020743) and IBM Instruments, Inc., for postdoctoral support (V.K.M.). The skilled assistance of R. D. Kendrick is gratefully acknowledged. We thank Dr. J. R. Lyerla for his interest and help in this work and Professor Martin Saunders for stimulating discussions.

Registry No. 2-Norbornyl cation, 24321-81-1.

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(15) Saunders, M. A.; Kates, M. R. *J. Am. Chem. Soc.* **1980**, *102*, 6867.

Stable Vinyl Cations. Direct Spectroscopic Observation of Vinyl-Substituted Vinyl Cations

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Vinyl cations, although well established as reactive intermediates[1a] and predicted to be rather stable thermodynamically,[1b] have been rather elusive toward direct spectroscopic observation. Attempts to generate vinyl cations via SbF_5-assisted heterolysis of α-arylvinyl halides resulted in attack of SbF_5 at the alkene π system and formation of σ complexes.[2] Protonation of alkynes under strongly acidic conditions also failed to give stable vinyl cation solutions;[3] rapid inter-[4] and intramolecular[5] sequential reactions took place instead. Hitherto the only spectroscopic evidence comes from treatment of α-alkynyl alcohols with superacids, leading to alkynylcarbenium ions, which may be regarded as vinyl cations if the allenic resonance structure is important.[6]

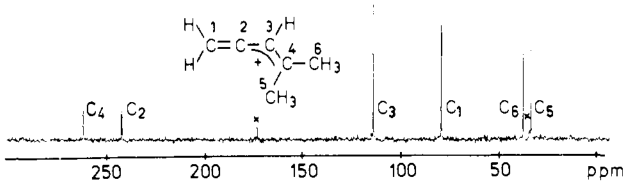
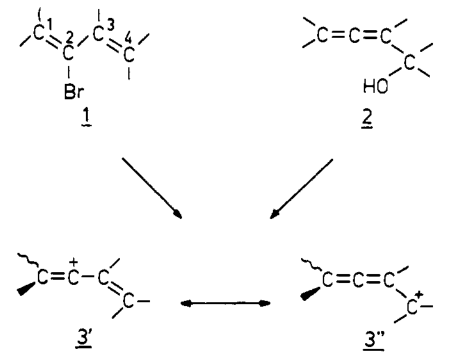


Figure 1. ^{13}C NMR spectrum of cation **3a** in SO_2ClF/SO_2F_2 (2:1) at −120 °C. Peaks marked × are due to CD_3COCl used as capillary lock.

We now report the first generation and NMR spectroscopic observation of α-vinyl-substituted vinyl cations **3**, which have previously been encountered as short-lived intermediates.

Grob and Spaar studied solvolysis reactions of 2-bromo-1,3-butadienes and found particularly large rate enhancements through methyl groups at C_4, in accord with intermediate vinyl cations **3′** ↔ **3″**.[7] Reactions of α-allenyl alcohols **2** with aqueous acid to give α,β-unsaturated ketones were also suggested to proceed via vinyl cations **3**.[8] Since conjugated double bonds are more stable than cumulated double bonds, vinyl cations **3** can be expected to form more readily from **2** than from **1**.



Clean solutions of **3a–c** in SO_2ClF/SO_2F_2 were obtained by reaction of alcohols **2a–c**[9] with SbF_5 using Saunders' "molecular beam" method.[10] The ^{13}C NMR spectra (Table I) were recorded at −120 °C and assigned by off-resonance and proton-coupled spectra (Figure 1). Single-frequency proton-decoupled spectra were used to confirm the assignments.

In all cations, C_2 and C_4 absorb at very low field, indicating location of positive charge at these positions. Contribution of both resonance structures **3′** and **3″** is thus confirmed. The small chemical shift difference between C_3 in **3** and **2** shows that this position does not carry significant charge. The C_1 resonances are also quite similar in cations **3** and precursors **2**, since the C_1C_2 π system cannot interact with the electron-deficient orbital at C_2. Hindered rotation around the C_3–C_4 bond is responsible for the nonequivalence of C_5 and C_6.

Small, but significant, effects on chemical shifts are generated by methyl substitution at C_1. The shift of C_1 corresponds to the normal α^{σ}–CH_3 effect in allenes ($\simeq$10 ppm/CH_3 group)[11] and is almost identical for alcohols **2a–c** and cations **3a–c**. While C_3 is practically unaffected by C_1 substituents, the chemical shifts of C_2 and C_4 show opposite trends in series **2** and **3**. In the alcohols **2**, C_1-methyl groups exert the normal β^{π}–CH_3 effect on C_2 ($\simeq$−3 ppm/CH_3 group) in allenes[11] and do not influence the remote C_4. In cations **3**, however, C_2 is deshielded and C_4 is shielded by methyl groups at C_1. CC hyperconjugation, which is more effective than CH hyperconjugation, can account for this effect since the C_1–CH_3 bond is ideally oriented (dihedral angle of 0°) for interaction with

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(1) (a) Stang, P. J.; Rappoport, Z.; Hanack, M.; Subramanian, L. R., "Vinyl Cations"; Academic Press: New York, 1979. (b) Mayr, H.; Schneider, R.; Wilhelm, D.; Schleyer, P. v. R. *J. Org. Chem.*, in press.

(2) Siehl, H.-U.; Hanack, M. *J. Am. Chem. Soc.* **1980**, *102*, 2686.

(3) Ferrocenyl-stabilized vinyl cations are accessible in this way and have been characterized by ^{1}H NMR spectroscopy: Abram, T. S.; Watts, W. E. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1522.

(4) Olah, G. A.; Staral, J. S.; Spear, R. J.; Liang, G. *J. Am. Chem. Soc.* **1975**, *97*, 5489.

(5) Olah, G. A.; Mayr, H. *J. Am. Chem. Soc.* **1976**, *98*, 7333; **1978**, *100*, 6544.

(6) Richey, H. G., Jr.; Philips, J. C.; Rennick, L. E. *J. Am. Chem. Soc.* **1965**, *87*, 1381. Richey, H. G., Jr.; Rennick, L. E.; Kushner, A. S.; Richey, J. M.; Philips, J. C. *Ibid.* **1965**, *87*, 4017. Pittman, C. U., Jr.; Olah, G. A. *Ibid.* **1965**, *87*, 5632. Olah, G. A.; Spear, R. J.; Westerman, P. W.; Denis, J.-M. *Ibid.* **1974**, *96*, 5855.

(7) Grob, C. A.; Spaar, R. *Helv. Chim. Acta* **1970**, *53*, 2119.

(8) Gelin, R.; Gelin, S.; Albrand, M. *Bull. Soc. Chim. Fr.* **1972**, 720. Olsson, L.-I.; Claesson, A.; Bogentoft, C. *Acta Chem. Scand.* **1973**, *27*, 1629.

(9) Alcohols **2a–c** were prepared by a standard procedure: Cowie, J. S.; Landor, P. D.; Landor, S. R. *J. Chem. Soc., Perkin Trans. 1*, **1973**, 720.

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

(11) Stothers, J. B. "Carbon-^{13}NMR Spectroscopy"; Academic Press: New York, 1972; p 76.

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