studies in this laboratory[15] indicate that **1d** has one-fourth to one-half the potency of **1a** in mice, but with a much shorter duration of action, whereas the 8α metabolite **1e** is much less active. These findings in man confirm our previous postulates, based on *in vitro* studies,[2e,f] that Δ⁹-THC is primarily metabolized by allylic hydroxylation at either the 8 or 11 position, followed by dihydroxylation to produce the 8,11-dihydroxy metabolite, and lends weight to the interesting speculations of Ben-Zvi, *et al.*,[14] that the cumulative effect of smoking marihuana may be based on a number of psychologically active cannabinoids derived from microsomal hydroxylation of Δ⁹-THC. The number of these metabolites found in biological fluids or tissues after *in vivo* metabolism in animals or man, often with similar R_f values by thin layer chromatography, indicates that identifications made by this useful technique must be regarded as tentative until confirmed by more rigid techniques such as gas–liquid chromatography combined with mass spectrometry.

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Monroe E. Wall,* Dolores R. Brine, Colin G. Pitt
Chemistry and Life Sciences Division, Research Triangle Institute
Research Triangle Park, North Carolina 27709

Mario Perez-Reyes
Department of Psychiatry
University of North Carolina School of Medicine
Chapel Hill, North Carolina 27514

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Deuterium Labeling as a Probe for Signal Assignments and Mechanistic Studies by ^{13}C Nuclear Magnetic Resonance. Cationic Rearrangements in Polycyclic Systems[1]

Sir:

Initially, D-labeled compounds were utilized in ^{13}C studies as assignment aids[2] or to simplify the analysis of complex spin systems[3] since the operating conditions led either to the "disappearance" of the signal(s) for the deuterated carbon or restricted the observable effects to the absorption of that carbon. With Fourier-transform operation and proton noise-decoupling, however, the effects of a single deuterium atom are readily detected at neighboring carbons because of coupling and geminal isotope shifts.[4] In general,[5] $J_{CCCH} > J_{CCH}$ and, since $J_{CD} = J_{CH}$ (6.5), both vicinal and geminal $^{13}C-^{2}H$ couplings are observable; also in favorable cases vicinal coupling is identifiable because of the dihedral angle dependence. Thus, several features in ^{13}C spectra of ^{2}H-labeled species are monitors of the label and are readily utilized for structural and mechanistic purposes as illustrated below.

The spectrum of camphor-*3-exo-*d_1 exhibits a triplet for C-5 by vicinal coupling between C-5 and 3-exo-D, as well as the expected changes in the C-3 absorption, whereas C-7, also vicinal, is little affected; upon introduction of a 3-endo deuterium, the C-7 signal becomes a triplet. Thus, the vicinal interactions display the expected stereospecificity. The corresponding $^{13}C-^{1}H$ couplings for C-7 in hexachloronorbornenes are 9 and 0 Hz.[6] Carbons geminal to deuterium exhibit isotope shifts of 0.12 ± 0.04 ppm that are upfield for sp^3 carbons but downfield for carbonyl carbon.[7]

The assignments for the four 5,6-dimethylnorbornan-2-ones are straightforward with the exception of the C-4, C-5, and C-6 signals. This problem is resolved, however, by base-catalyzed D exchange of the C-3 proton(s). The spectra of the monodeuterated ketones reveal a 0.1-ppm upfield shift for one of these signals and a significantly broadened band for another, while the third is unaffected; thus the assignments to C-4, C-5, and C-6, respectively, were completed.

The careful selection of operating parameters leads to total integrated intensities of partially deuterated methyl and/or methylene carbons equal to those for nonlabeled materials since the Overhauser enhancement from proton decoupling is independent of the number of hydrogens.[8] The decrease in intensity for the *residual* CH absorption of a partially deuterated methine carbon gives a direct measure of the extent of deuteration. The $^{13}C-^{2}H$ induced triplets do not overlap the residual $^{13}C-^{1}H$ absorptions because of the isotope shift and coupling. If dipole–dipole relaxation is dominant for several carbons their integrated intensities are equal. For such systems the ^{2}H content at individual carbons can be assayed. These may be summed and compared with mass spectrometric data for total ^{2}H content as a check, and, in certain cases, proton spectra provide an independent measure for specific centers. Thus, with both quantitative and qualitative assay of the ^{2}H label(s), ^{13}C nmr is a new mechanistic probe.

Rearrangements of the norbornyl skeleton during acetolysis have been investigated with the aid of ^{14}C and ^{3}H labeling, and the tracer distribution determined by stepwise degradation of the product.[9,10] Similar information is obtained much more readily by direct observations with ^{13}C nmr. Brosylates **1** and **2**,

(1) Part XXIV in the series ^{13}C Nuclear Magnetic Resonance Studies. Part XXIII: V. Dave, J. B. Stothers, and E. W. Warnhoff, *Can. J. Chem.*, **50**, 2475 (1972).

(2) W. G. Schneider and H. Spiesecke, *J. Chem. Phys.*, **35**, 731 (1961); H. J. Reich, M. Jautelat, M. T. Messe, F. J. Weigert, and J. D. Roberts, *J. Amer. Chem. Soc.*, **91**, 7445 (1969).

(3) F. J. Weigert and J. D. Roberts, *ibid.*, **89**, 2967 (1967).

(4) Y. K. Grishin, N. M. Sergeyev, and Y. A. Ustymjuk, *Mol. Phys.*, **22**, 711 (1971); R. A. Bell, C. L. Chan, and B. G. Sayer, *J. Chem. Soc., Chem. Commun.*, 67 (1972).

(5) J. B. Stothers, "Carbon-13 NMR Spectroscopy," Academic Press, New York, N. Y., 1972.

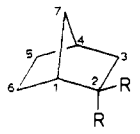
(6) K. L. Williamson, D. R. Clutter, and D. Bencivenga, Abstracts, 163rd National Meeting of the American Chemical Society, Boston, Mass., April 1972, No. ORGN-112.

(7) G. E. Maciel, P. D. Ellis, and D. C. Hofer, *J. Phys. Chem.*, **71**, 2160 (1967).

(8) K. F. Kuhlmann, D. M. Grant, and R. K. Harris, *J. Chem. Phys.*, **52**, 3449 (1970).

(9) J. D. Roberts, C. C. Lee, and W. H. Saunders, Jr., *J. Amer. Chem. Soc.*, **76**, 4501 (1954).

(10) C. C. Lee and L. K. M. Lam, *ibid.*, **88**, 2831 (1966); (b) C. C. Lee, B. S. Hahn, and L. K. M. Lam, *Tetrahedron Lett.*, 3049 (1969).



1 R = OBs, R' = D

2 R = D, R' = OBs

3 R = OAc R = H

prepared from norborneol-*2-endo-d*[11] (0.99–1.0 *d* by combustion analysis), were solvolyzed (NaOAc buffer) under the conditions in Table I; the ^{13}C spectra of the

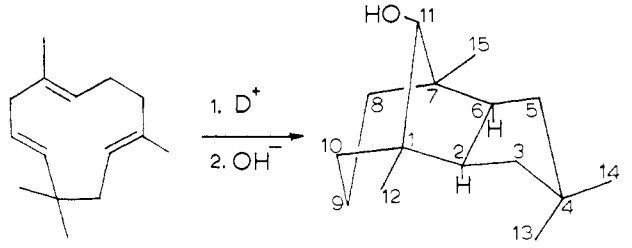
Table I. ^{2}H Distribution by ^{13}C Nmr in **3** from Acetolysis of **1** and **2**

Substrate (mmol)	Temp, °C	Time, hr	—% D in 3 (±3%)— C-1	C-2	C-6
1[a] (2.25)	45	24	46	46	11
2[a] (4.24)	Reflux	20	38	38	22

[a] With tritiated analogs of **1** and **2**, average values for C-1, C-2, and C-6 of 40.1, 38.2, and 20.5 from **1**, and 36.0, 37.7, and 25.6 from **2** were obtained.[10a]

norbornyl-*d* acetates clearly showed deuterium at C-1, C-2, and C-6 *only;* and integration gave the results in Table I. The *total* label scrambled to the remaining sites is known[10] to be <7% for **1** and <5% for **2**, and the amount at any *one* site would be below our limit of detectability (*ca.* 3%).[12]

In studies on the mechanisms of polyene cyclizations we have treated humulene (**4**) with D_2SO_4 to produce apollanol (**5**).[13] The extent of deuterium incorporation



4 **5**

depends on the experimental conditions, and a multilabeled product (**5**-d_n) from one such cyclization contained 13% d_0, 26% d_1, 34.5% d_2, 18% d_3, 6.5% d_4, 2% d_5 (total 1.85 *d*) by mass spectral analysis. Despite the complexity of the multideuteration, the ^{13}C spectra of the labeled and normal appollanol permitted identification of all labeled sites.

Owing to symmetry, the proton-decoupled ^{13}C spectrum of **5** contains only ten signals, which are readily assigned (ppm from TMS in C_6D_6) as 78.4 (C-11), 46.7 (C-2,6), 43.9 (C-3,5), 41.7 (C-1,7), 39.4 (C-4), 31.9 (C-8,10), 28.9 (C-14), 25.5 (C-13), 21.0 (C-12,15), 19.1 (C-9). Besides these signals, **5**-d_n exhibits triplets at 43.5, 31.4, and 20.6 ppm revealing deuterium at C-3(5), C-8(10), and C-12(15). Also, portions of the C-2(6), C-1(7), C-4, and C-9 absorptions show typical geminal isotope shifts of *ca.* 0.1 ppm; in fact, the major C-9 signal is shifted and there is a significant signal 0.2 ppm upfield from the normal peak signifying two geminal deuteriums. Further, the total intensity of the C-8(10) absorption shows that dideuteration occurs at this position. This fact, together with the shape of the C-9 absorption, confirms the methylene assignments. Intensity measurements revealed no detectable (<3%) deuterium at carbons 2(6), 9, 11, 13, 14, with the total content of 1.9 *d* distributed at the remaining sites as follows: CHD at C-3(5) (23%); CHD at C-8(10) (26%); CD_2 at C-8(10) (16%) and CH_2D at C-12(15) (16%); all values are ±3%.

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J. B. Stothers,* C. T. Tan
Department of Chemistry
University of Western Ontario, London, Canada

A. Nickon, F. Huang, R. Sridhar, R. Weglein
Department of Chemistry, The Johns Hopkins University
Baltimore, Maryland 21218

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^{13}C Nuclear Magnetic Resonance as a Monitor for Anionic Exchange Processes.[1] Remote Epimerization *via* Homoenolate Ions and Aryl D Exchange

Sir:

We wish to report the first example of epimerization *via* a homoenolate ion[2] at a center remote to a carbonyl group and to demonstrate how ^{13}C nmr greatly simplifies studies of anionic exchange.

In principle, *endo*-isocamphanone (**1**) and *exo*-isocamphanone (**2**)[3] should be interconvertible by alkali *via* the common homoenolate ion **3**, which could also lead to camphor (**4**).[4] Homoenolization in ketones **1**, **2**, and **4** is of added interest because each contains two enolizable protons, and the question arises whether their abstraction would preclude generation of higher energy homoenolate species. Demonstration of the compatibility of both processes within the same molecule would enhance the scope of homoenolization considerably.

Each of the ketones **1**, **2**, and **4** was heated at elevated temperatures in *t*-BuOK/*t*-BuOH, and the recovered ketone mixtures were analyzed by glpc. In addition

(11) B. L. Murr and J. A. Conkling, *J. Amer. Chem. Soc.*, **92**, 3462 (1970); J. A. Conkling, Ph.D. Dissertation, The Johns Hopkins University, 1969.

(12) We have similarly used ^{13}C nmr to study rearrangements in bridged polycyclic systems, and the results will be published elsewhere. (a) A. Nickon, H. Kwasnik, T. Swartz, R. O. Williams, and J. B. DiGiorgio, *J. Amer. Chem. Soc.*, **87**, 1613, 1615 (1965); (b) A. Nickon, G. D. Pandit, and R. O. Williams, *Tetrahedron Lett.*, 2851 (1967); (c) A. Nickon and G. D. Pandit, *ibid.*, 3663 (1968).

(13) (a) A. Nickon, T. Iwadare, F. J. McGuire, J. R. Mahajan, S. A. Narang, and B. Umezawa, *J. Amer. Chem. Soc.*, **92**, 1688 (1970); (b) A. Nickon, F. Y. Edamura, T. Iwadare, K. Matsuo, F. J. McGuire, and J. S. Roberts, *ibid.*, **90**, 4196 (1968); (c) A. Nickon and F. Y. Edamura, *J. Org. Chem.*, **35**, 1509 (1970).

(1) Part XXV in the series ^{13}C Nuclear Magnetic Resonance Studies. Part XXIV: J. B. Stothers, C. T. Tan, A. Nickon, F. Huang, R. Sridhar, and R. Weglein, *J. Amer. Chem. Soc.*, **94**, 8581 (1972).

(2) (a) A. Nickon and J. L. Lambert, *ibid.*, **84**, 4604 (1962); **88**, 1905 (1966); (b) A. Nickon, J. L. Lambert, and J. E. Oliver, *ibid.*, **88**, 2787 (1966).

(3) E. Demole, *Helv. Chim. Acta*, 47, 319 (1964).

(4) For examples of skeletal rearrangement *via* homoenolate ions, see (a) A. Nickon, H. Kwasnik, T. Swartz, R. O. Williams, and J. B. DiGiorgio, *J. Amer. Chem. Soc.*, **87**, 1615 (1965); (b) R. M. Coates and J. P. Chen, *Chem. Commun.*, 1481 (1970).