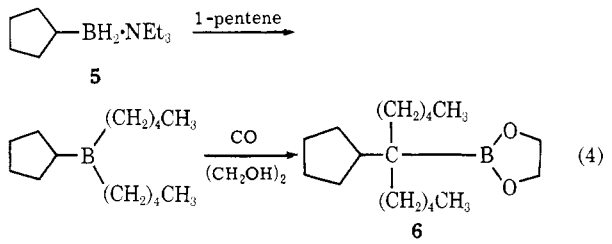
Table I. The Preparation and Characterization of Triethylamine–Monoalkylboranes[a]

Olefin	Triethylamine–monoalkylborane[b] Alcohol,[c,d] mmol	TME dehydroborated,[c] mmol	Dimethyl alkaneboronate[e] Yield, % Glpc	Yield, % Isolated	Bp, °C (mm)	n^{20}D
trans-3-Hexene	10.0	9.5	96	75	52–53 (15)	1.4075
2-Methyl-1-pentene	9.3	8.8	90	70	56–57 (15)	1.4092
Cyclopentene	9.6	10.0	98		*f*	
Cyclohexene	9.8	10.0	95	77	75–76 (17)	1.4375
2-Methyl-2-butene	9.5	9.5			*g*	
1-Methylcyclopentene	9.7	9.8	93	80	60–61 (15)	1.4290

[a] Prepared by the reaction of 10 mmol of thexylmonoalkylborane and 40 mmol of triethylamine. [b] All exhibit a strong, broad ir absorption centered at *ca.* 2350 cm^{-1} and satisfactory pmr spectra. The glpc yield of triethylamine was 100–105%. [c] By glpc. [d] Alcohol corresponds to the olefin used. Less than 0.5 mmol of 2,3-dimethyl-2-butanol and less than 0.1 mmol of 2,3-dimethyl-1-butanol were observed except with 2-methyl-1-pentene. In the case of 2-methyl-1-pentene, 1.0 mmol of 2,3-dimethyl-2-butanol was observed. [e] Satisfactory pmr and ir data were obtained. On oxidation, the corresponding alcohol was obtained in 100 ± 5% yields. [f] Triethylamine–cyclopentylborane was identified by the conversion in 70% to 2-(cyclopentyldi-*n*-pentylcarbinyl)-2-bora-1,3-dioxolane, bp 127–128° (0.7 mm); n^{20}D 1.4675. [g] Triethylamine–(3-methyl-2-butyl)borane was identified by the conversion in 72% to 2-[(3′-methyl-2′-butyl)dicyclopentylcarbinyl]-2-bora-1,3-dioxolane, bp 130–131° (0.8 mm); n^{20}D 1.4996.

of the methanolysis product from **3** produces pure **4**[7] in 80% yield, thereby providing a new, low-temperature route to such boronic acid esters. In marked contrast with the corresponding trimethylamine or pyridine complexes, which show little tendency to hydroborate at 25°, triethylamine–monoalkylboranes hydroborate olefins at 25° at reasonable rates. Addition of 1.4 g (20 mmol) of 1-pentene to a crude mixture containing 10 mmol of triethylamine–cyclopentylborane (**5**) results in the uptake of greater than 90% of the 1-pentene in 16 hr at 25°. Carbonylation of the reaction mixture in the usual manner[8] yields the corresponding boronate[9] (**6**) in 70% yield (eq 4), bp 127–128° (0.7 mm); n^{20}D



(4)

1.4675. This result should be compared with our recent observation that the reaction of thexylcyclopentylborane with 2 equiv of 1-butene results in the displacement of only 1% of the thexyl group, failing to produce the corresponding cyclopentyldi-*n*-butylborane.[10] The hydroboration with triethylamine–monoalkylboranes can be greatly accelerated by carrying out the reaction in hexane in the presence of boron trifluoride etherate. In the absence of olefins, this reaction provides free monoalkylboranes in a manner similar to our recent procedure using pyridine–monoalkylboranes.[5]

The present novel, convenient synthesis of triethylamine–monoalkylboranes makes these derivatives easily available for the first time and should greatly facilitate the application of organoborane chemistry to organic synthesis.

(7) All isolated dimethyl alkaneboronates were identified and characterized by glpc analysis of the oxidation products, pmr, ir, boiling points, and refractive indices as summarized in Table I.

(8) H. C. Brown, E. Negishi, and S. K. Gupta, *J. Amer. Chem. Soc.*, **92**, 6648 (1970).

(9) The product yielded correct elemental analyses and spectral data.

(10) C. F. Lane and H. C. Brown, *J. Organometal. Chem.*, **34**, C29 (1972).

(11) Postdoctoral Research Associate on Grant No. DA 31-124 ARO(D) 453, supported by the U. S. Army Research Office (Durham).

(12) Graduate Research Assistant on Grant No. GM 10937, supported by the National Institutes of Health.

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The Use of Proton and Carbon-13 Nuclear Magnetic Resonance for Assignment of the Glycosylation Site in 3- and 5-Substituted 1-β-D-Ribofuranosyl-1,2,4-triazoles

Sir:

We report here the novel use of both ^{1}H (pmr) and ^{13}C (cmr) nmr to establish the glycosylation site in 1-β-D-ribofuranosyl-1,2,4-triazoles. To our knowledge, this is the first report of cmr used in this manner.

Several substituted 1-β-D-ribofuranosyl-1,2,4-triazoles have recently been shown to exhibit broad spectrum antiviral activity in tissue culture and in animal systems.[1,2] These nucleosides were prepared by both the silylation–glycosylation and the acid-catalyzed procedures which provided both the 3- and 5-substituted isomeric products.[3] The classical utilization of uv spectra to assign the position of ribose attachment was of no avail, since these compounds showed weak absorption.

The results of our nmr experiments are summarized in Table I. The pmr spectrum of 1,2,4-triazole base I has been reported and is a singlet at −8.33 ppm.[4a] The cmr spectrum, as previously noted,[4b] also shows

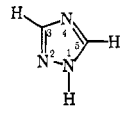
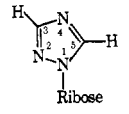
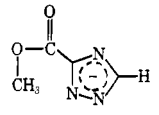
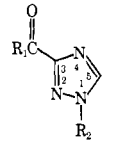
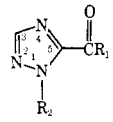
(1) R. W. Sidwell, J. H. Huffman, G. P. Khare, L. B. Allen, J. T. Witkowski, and R. K. Robins, *Science*, in press.

(2) J. H. Huffman, J. T. Witkowski, R. K. Robins, R. W. Sidwell, G. P. Khare, W. B. Jolley, L. N. Simon, L. P. Gebhardt, and D. G. Streeter, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **31**, Abstracts 2035, 2036, 2037, 2038 (1972).

(3) J. T. Witkowski, R. K. Robins, and R. W. Sidwell, Abstracts, 163rd National Meeting of the American Chemical Society, Boston, Mass., April 1972, No. MEDI 19.

(4) (a) R. Jacquier, M-L. Roumestant, and P. Viallefont, *Bull. Soc. Chim. Fr.*, 2630 (1967); (b) F. J. Weigert and J. D. Roberts, *J. Amer. Chem. Soc.*, **90**, 3543 (1968).

Table I. ^{1}H and ^{13}C Chemical Shifts of 3- and 5-Substituted 1-β-D-Ribofuranosyl-1,2,4-triazoles

Compound	R_1	R_2	Pmr[a] H_3	Pmr[a] H_5	Pmr[a] H_1'	Pmr[a] $\lvert J_{H_1'-H_2'}\rvert$	Cmr[b] C_3	Cmr[b] C_5	Cmr[b] -C(=O)-
 I			−8.33	−8.33			−9.3	−9.3	
 II			−8.08	−8.80	−5.85	3.7	−14.6	−6.8	
 III							−15.9	−12.9	−24.8
 Class A	OCH_3	CH_3[c]		−8.67			−16.5	−8.8	−22.8
	OCH_3	β-D-Ribofuranosyl		−8.99	−5.90	3.7	−17.0	−8.2	21.6
							(−17.9)	(−5.9)[d]	
	NH_2	β-D-Ribofuranosyl		−8.91	−5.85	3.8	−19.8	−7.7	−23.2
 Class B	OCH_3	CH_3[c]	−8.11				−13.7	−7.1	−20.8
	OCH_3	β-D-Ribofuranosyl	−8.29		−6.54	2.9	−13.6	−7.5	−20.3
							(−14.9)	(−8.9)[d]	
	NH_2	β-D-Ribofuranosyl	−8.16		−6.77	3.0	−12.9	−10.2	−21.4

[a] Pmr spectra of 10% DMSO solutions were obtained on a 60-MHz Hitachi Perkin-Elmer R20A nmr spectrometer with a probe temperature of 34°. Chemical shifts are reported in ppm relative to internal DSS. [b] Cmr spectra of 50% DMSO solutions were obtained on a Bruker HX-90 nmr spectrometer operating at 22.62 MHz in the Fourier Transform Mode at a probe temperature of 30°. Chemical shifts are reported in ppm relative to an external C_6F_6 capillary ($\delta_{C_6H_6} = \delta_{C_6F_6(ext)} - 9.9$ ppm). [c] Obtained by methylation: methyl 1-methyl-1,2,4-triazole-3-carboxylate, mp 129–131°; methyl 1-methyl-1,2,4-triazole-5-carboxylate, mp 74–76°. [d] Predicted values of chemical shifts using α and β of 7 and 2 ppm, respectively, for the methyl ester derivatives.

only one resonance at −9.3 ppm which is the A part of an AX_2 multiplet due to spin–spin coupling of the carbon atoms with the ring protons with $|J_{CH}| = 205$ Hz and $|J_{CNCH}| = 10$ Hz. The magnetic equivalence of both nuclei is indicative of rapid exchange of the N–H proton between the three nitrogens. This equivalence is, however, destroyed upon ribosylation at N_1 (II)[5] as is shown in Table I.

In the pmr spectrum of the majority of 3- (class A) and 5- (class B) substituted triazole nucleosides, the ring proton resonance had a comparable chemical shift to either the H_3 or H_5 resonance of the unsubstituted triazole nucleoside II. Similarly, the cmr spectrum of these compounds showed two resonances for the ring carbons which had similar chemical shift to the C_3 and C_5 resonances of the ribosylated triazole II. The two carbon resonances in a substituted triazole nucleoside could easily be distinguished because the unsubstituted carbon showed large coupling with the proton, $|J_{CH}| \cong 205$ Hz, while the substituted carbon showed only a small long-range coupling constant, $|J_{CNCH}| \cong 10$ Hz.

The actual assignment of each class as a 3- or 5-substituted triazole nucleoside was deduced in the following manner. As can be seen in Table I, the aromatic protons of the class A compounds are at a significantly lower field than those for the class B compounds. This downfield shift of the base proton is characteristic of 1,3-disubstituted triazoles[4a] and is consistent with the downfield shift of the H_8 of purines upon N_9 ribosylation.[6] More direct information about the structure of the two isomeric forms can be obtained from ^{13}C spectra of the base carbons. The chemical shifts of these carbons were compared to those of the 3-carbomethoxy-1,2,4-triazole anion which was formed by neutralization of the appropriate substituted triazole by LiOH in DMSO. Using the previously reported α and β substitution shifts observed in other heterocyclic systems upon comparison of a neutral species with the anionic form,[7-9] reasonable agreement between the predicted and experimental values could be obtained only if the indicated assignment of the two isomers was used (see Table I).

Although the structural assignment based only on the behavior of ^{1}H and ^{13}C resonances of the base itself appeared to be self-consistent, several other nmr experiments should be noted which add credibility to this assignment. One of the most striking differences in the pmr spectrum between classes A and B is a large

(5) J. T. Witkowski and R. K. Robins, *J. Org. Chem.*, **35**, 2635 (1970).

(6) C. D. Jardetzky and O. Jardetzky, *J. Amer. Chem. Soc.*, **82**, 222 (1960).

(7) R. J. Pugmire and D. M. Grant, *ibid.*, **90**, 697 (1968).

(8) R. J. Pugmire and D. M. Grant, *ibid.*, **90**, 4232 (1968).

(9) R. J. Pugmire, D. M. Grant, R. K. Robins, and L. B. Townsend, *ibid.*, in press.

downfield shift of the anomeric proton for the latter. This shift is attributed to the close proximity of the anisotropic carbonyl group. The same effect has been observed in other nucleosides with similarly oriented carboxamide substituents.[10]

Spatially the relationship of the ribose ring to the base protons of classes A and B is similar to the situation for H_6 and H_5 of pyrimidine nucleosides. We have observed a $|J_{H_3-H_{1'}}|$ of ~0.6 Hz for class B but not class A compounds in agreement with the findings of Hruska[11] for uridine, 2'-deoxyuridine, and others, provided the anti conformation is assumed.

At a given concentration of added purine, the H_3 resonances of class B compounds were shifted to a higher field than the H_5 resonance of class A compounds which is similar to the case for H_5 and H_6 of pyrimidine nucleosides.[12] This is due to the greater overlap with a costacked diamagnetic purine ring at the proton furthest from the glycosylation site. Finally, assignment of the structure of 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide (virazole) was confirmed by single-crystal X-ray studies by Prusiner and Sundaralingam.[13]

The use of nmr, especially ^{13}C, provides a general unequivocal method for the assignment of structures of highly substituted heterocyclic ring compounds which exhibit very little uv absorption. The efficiency of this method may be extremely advantageous in lieu of more tedious direct chemical procedures.

Acknowledgment. We thank Mr. E. B. Banta for technical assistance and Drs. R. J. Pugmire and Sunney I. Chan for helpful discussions.

(10) G. R. Revankar and L. B. Townsend, *J. Heterocycl. Chem.*, **7**, 1329 (1970).
(11) F. E. Hruska, *Can. J. Chem.*, **49**, 2111 (1971).
(12) M. P. Schweizer, S. I. Chan, and P. O. P. Ts'o, *J. Amer. Chem. Soc.*, **87**, 5241 (1965).
(13) P. Prusiner and M. Sundaralingam, personal communication.

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Nuclear Magnetic Resonance Studies of Long-Range Carbon-13 Spin Couplings

Sir:

Carbon-13 nuclear magnetic resonance spectroscopy is rapidly becoming an important probe in determining molecular structure. Although many data have been accumulated relating the factors that influence the chemical shift of carbon-13 nuclei,[1] much less is known about the factors that affect the magnitude of the spin–spin coupling constants. This is especially true of long-range carbon-13 spin interactions with fluorine.

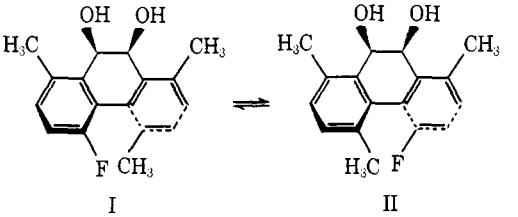
In order to gain insight into the spin coupling mechanisms which contribute to carbon-13 nuclear spin coupling, a series of bridged biphenyls was examined. This system was chosen because of its proven utility in assessing the importance of through-space interactions in long-range coupling between H–F and F–F nuclei.[2] It was further hoped that the stereochemical dependence demonstrated in the bridged biphenyls for H–F and F–F coupling would prove useful in understanding $^{13}C-^{19}F$ spin interactions. We now wish to report that carbon-13 nuclei do exhibit long-range coupling to fluorine and that the coupling displays the same stereochemical dependence as observed in H–F and F–F long-range coupling.

The 15.1-MHz $^{13}C-\{^1H\}$ proton noise-decoupled spectrum of 1,4,8-trimethyl-5-fluorophenanthrene (**1**-CH_3) exhibits three methyl carbon resonances at 20.0, 20.2, and 24.0 ppm in addition to aromatic carbon resonances.[3,4] The 24.0-ppm peak exhibits a $^{13}C-^{19}F$ coupling constant of 24.0 Hz and is assigned to the C_4 methyl carbon. This extraordinarily large five-bond $^{13}C-^{19}F$ coupling provides the first compelling evidence that a through-space mechanism can be operative in carbon-13 coupling.[5] Saturation of the 9,10 bond, as in *cis*-1,4,8-trimethyl-5-fluoro-9,10-dihydro-9,10-phenanthrenediol (**2**-CH_3), results in a marked decrease in this coupling constant: $^5J_{C-F} = 15.7$ Hz.[6,7] Oxidation of **1**-CH_3 to 1,4,8-trimethyl-5-fluoro-9,10-phenanthrenequinone (**3**-CH_3) resulted in a similar decrease in the coupling constant: $^5J_{C-F} = 16.1$ Hz. These coupling constants as well as those reported earlier for H–F and F–F couplings in the bridged biphenyl system are summarized in Table I.

Dreiding models of **1**-CH_3, **2**-CH_3, and **3**-CH_3 indicate that severe steric interactions between the groups at the 4 and 5 positions result in large deviations from planarity. This effect is reflected in the chemical shift of the methyl carbons at the four position (*vide infra*).[8] As a result of differences in torsional strains, deviations

(1) (a) H. J. Reich, M. Jautelat, M. T. Messe, F. J. Weigert, and J. D. Roberts, *J. Amer. Chem. Soc.*, **91**, 7445 (1969); (b) A. J. Jones, D. M. Grant, M. W. Winkley, and R. K. Robins, *ibid.*, **92**, 4079 (1970), and references therein.

(2) K. L. Servis and F. R. Jerome, *ibid.*, **93**, 1535 (1971).
(3) The authors express their appreciation to Dr. Douglas Dorman at the California Institute of Technology for obtaining this spectrum.
(4) (a) The syntheses of **1**-CH_3, **2**-CH_3, **3**-CH_3, and **4**-CH_3 have been reported previously; see ref 2. (b) ^{13}C chemical shifts are reported in parts per million downfield from internal tetramethylsilane. **1**-CH_3 was measured in dioxane with dioxane as internal standard. **2**-CH_3 and **3**-CH_3 were measured in chloroform with reference TMS as internal standard. The conversion to reference TMS was made by the assumption: $\delta^{ref}_{TMS} = \delta^{ref}_{dioxane} - 69.0$ ppm.
(5) (a) The largest previously reported five-bond $^{13}C-F$ coupling was less than 1 Hz: F. J. Weigert and J. D. Roberts, *J. Amer. Chem. Soc.*, **93**, 2361 (1971). (b) Typical values for geminal $^{13}C-^{19}F$ coupling constants are 20–40 Hz: J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 2, Pergamon Press, New York, N. Y., 1966, p 962.
(6) We would like to thank Dr. William Jankowski of Varian Associates for obtaining the ^{13}C nmr spectra of **2**-CH_3 and **3**-CH_3.
(7) The ^{13}C nmr spectrum of **2**-CH_3 displayed very broad absorptions for the methyl carbons at the 1 and 8 positions. This appears to be due to the slow interconversion of the two diastereomeric forms I and II.



I II

The slow interconversions also result in the observation of two different fluorine resonance absorptions of unequal intensities at 31.26 and 32.86 ppm upfield from 1,1,1-trichloro-2,2,2-trifluoroethane in the 94.1-MHz nmr spectrum.
(8) This effect is also reflected in the ^1H nmr spectra. As the molecule deviates from planarity, the methyl group at the 4 position moves into the positive cone of the other aromatic ring and an upfield shift of the methyl hydrogens results ($\delta_{4\text{-}CH_3}{}^{2\text{-}CH_3} - \delta_{4\text{-}CH_3}{}^{1\text{-}CH_3} = 0.37$ ppm).