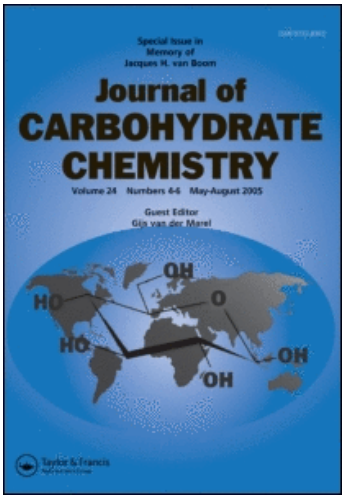


Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

^{1}H and ^{13}C NMR Spectroscopy of Stereoisomeric 2'-deoxy-*C*-Nucleosides

Uli Hacksell[ab]; Jane Chi-Ya Cheng[a]; G. Doyle Daves Jr.[a]

[a] Department of Chemistry, Lehigh University, Bethlehem, Pennsylvania, USA [b] Department of Organic, Pharmaceutical Chemistry Biomédical Center, University of Uppsala, Uppsala, Sweden

To cite this Article Hacksell, Uli , Cheng, Jane Chi-Ya and Daves Jr., G. Doyle(1986) '^{1}H and ^{13}C NMR Spectroscopy of Stereoisomeric 2'-deoxy-*C*-Nucleosides', Journal of Carbohydrate Chemistry, 5: 2, 287 — 297

To link to this Article: DOI: 10.1080/07328308608062967

URL: http://dx.doi.org/10.1080/07328308608062967

J. CARBOHYDRATE CHEMISTRY, 5(2), 287-297 (1986)

^{1}H AND ^{13}C NMR SPECTROSCOPY OF STEREOISOMERIC 2'-DEOXY-C-NUCLEOSIDES

Uli Hacksell[x+], Jane Chi-Ya Cheng[x] and G. Doyle Daves, Jr.[x*]

[x]Department of Chemistry
Lehigh University
Bethlehem, Pennsylvania 18015, USA

and

[+]Department of Organic Pharmaceutical Chemistry
Biomedical Center, University of Uppsala, S-751 23
Uppsala, Sweden

Received December 24, 1985 - Final Form February 26, 1986

ABSTRACT

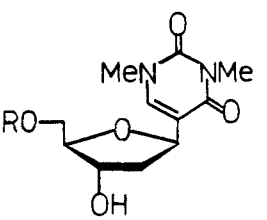
Eleven furanosyl 2'-deoxy-C-nucleosides with β-D-erythro, α-D-erythro and β-D-threo configurations have been studied by ^{1}H and ^{13}C NMR spectroscopy recorded in $CDCl_3$ and/or DMSO-d_6. Results obtained indicate that each of the three stereoisomeric configurations studied are identifiable by ^{1}H and ^{13}C NMR spectroscopy using a combination of coupling constant and chemical shift criteria.

INTRODUCTION

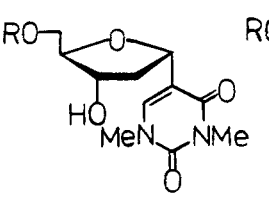
C-Nucleosides are a growing class of substances which possess diverse biological effects and hold significant therapeutic

promise including use in treatment of cancer.[1] Several syntheses of 2'-deoxy C-nucleosides have been reported;[2-10] however, to our knowledge, relatively little is known concerning the nuclear magnetic resonance (NMR) spectrometric properties of these compounds. In contrast, numerous reports on ^1H NMR spectrometry of the corresponding N-nucleosides have appeared during the past two decades.[11]

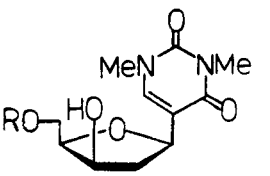
During exploration of palladium(II) chemistry for use in C-nucleoside and glycoside synthesis,[12-21] compounds 1-3 were prepared.[16-18]



1a-d



2a-c



3a-d

a: R=H
b: R=CH_2OCH_3
c: R=Si(i-Pr)$_3$
d: R=$CH_2OCH_2CH_2OCH_3$

These structures represent three of four possible stereoisomeric substitutent arrangements of a furanosyl D-2'-deoxy-C-nucleoside, and thus, they offer the opportunity to correlate NMR spectrometric properties with 2'-deoxy-C-nucleoside stereochemistry. In the present study ^1H and ^{13}C NMR spectra of compounds 1-3 have been analyzed and implications for solution conformations of the 2'-deoxy-C-nucleosides considered.

RESULTS AND DISCUSSION

The conformational flexibility of five membered rings in solution[22] makes it difficult to deduce stereochemical relationships between vicinal hydrogens from observed $^3J_{H,H}$ coupling constants since these are weighted averages of the coupling constants for the respective hydrogens of various co-existing conformers present at equilibrium. Fortunately, however, the furanose ring in β-N and C-nucleosides assumes mainly two narrow pseudorotational ranges, defined by Altona and Sundaralingam[23-25] as N and S forms.[26] This makes it possible to analyze ^{1}H NMR spectra of nucleosides and nucleotides[27-29] in terms of an equilibrium between N- and S-conformers.

Two different trial analyses of the ^{1}H NMR spectrum of 1a (denoted A and B, Table 1) were made since it was unclear which of the two $C_{2'}$-hydrogens (α or β) to assign to the multiplet at δ 1.73 ppm. Assuming that the ^{1}H NMR-spectrum of 1a in DMSO reflects a time average of equilibrating N and S conformers, analyses A and B can be compared with theoretical coupling constants calculated for these pseudorotational ranges.[24] Whereas analysis A is consistent with the expected equilibrium of N and S conformers, analysis B does not accord with any such equilibrium, nor with either the N or S forms alone and can be rejected.

In accordance with analysis A (Table 1), the multiplets at δ 1.73 and δ 2.03 in the ^{1}H NMR spectrum of 1a are assigned to $H_{2'\beta}$ and $H_{2'\alpha}$, respectively. This implies that the pyrimidinyl aglycone, through its diamagnetic anisotropy, deshields the trans positioned $H_{2'\alpha}$.[30] Interestingly, a similar effect was observed when the chemical shifts of $H_{2'}$ in α- and β-pseudouridine were compared.[31] Similarly, $H_{2'\beta}$ is shifted upfield of $H_{2'\alpha}$ in 2'-deoxyuridine, 2'-deoxycytidine and 2'-deoxythymidine.[32,33] The anisotropy of the pyrimidinyl substituent made assignments in spectra of compounds 1-3 straightforward (Tables 2 and 3).

TABLE 1

Analysis of Coupling Constants (^3J) in the ^1H NMR Spectrum of 1,3-Dimethyl-2'-deoxypseudouridine (1a)

	Experimental[a] (Hz)		Calculated[c] (Hz)
	A[b]	B[b]	
$J_{1',2'\alpha}$	5.8	9.8	6.0
$J_{1',2'\beta}$	9.8	5.8	8.1
$J_{2'\alpha,3'}$	2.1	5.5	2.8
$J_{2'\beta,3'}$	5.5	2.1	5.6
$J_{3',4'}$	2.3	2.3	2.4

a. Recorded in DMSO-d_6.
b. Analysis confirmed by spin-spin simulation. Coupling constants based on assignment of the multiplet at δ 1.73 ppm to $H_{2'\beta}$ (A) or to $H_{2'\alpha}$ (B).
c. Coupling constants derived by assuming a 78%S - 22%N conformational equilibrium; theoretical coupling constants for the pure N- and S-forms were taken from reference 24.

TABLE 2
^{1}H NMR Chemical Shifts δ (ppm) of 2'-Deoxy-C-Nucleosides

Comp.	Solvent	$H_{1'}$	$H_{2'\alpha}$	$H_{2'\beta}$	$H_{3'}$	$H_{4'}$	$H_{5'},H_{5''}$	H_6	Other
1a	DMSO-d_6	4.81	2.03	1.73	4.08	3.66	3.40	7.64	NMe's, 3.29, 3.14
1b	DMSO-d_6	4.85	2.09	1.78	4.09	3.79	3.48	7.55	NMe's, OMe, 3.30, 3.27, 3.15; OCH_2O, 4.58
	$CDCl_3$	5.05	2.45	1.87	4.31	4.05	3.65	7.36	NMe's, OMe, 3.36 (6H), 3.31; OCH_2O, 4.65
1c	$CDCl_3$	5.01	2.45	1.87	4.45	4.03-3.70		7.32	NMe's, 3.36, 3.34; $SiCH(CH_3)_2$, 1.06
1d	$CDCl_3$	5.09	2.42	1.99	4.36	4.02	3.85-3.50	7.32	NMe's, Me, 3.377, 3.383, 3.32; OCH_2O, 4.75; OCH_2CH_2O, 3.82-3.50
2a	DMSO-d_6	4.73	1.72	2.42[a]	4.13	3.82	3.44	7.60	NMe's, 3.31, 3.15
2b	DMSO-d_6	4.77	1.75	2.42[a]	4.26-3.80		3.50	7.60	NMe's, OMe, 3.32, 3.25, 3.15; OCH_2O, 4.57
	$CDCl_3$	4.85	1.98	2.68	4.45-4.12		3.59	7.33	NMe's, OMe, 3.41, 3.37, 3.34; OCH_2O, 4.68
2c	$CDCl_3$	4.84	1.87	2.66	4.53-3.91		3.70	7.24	NMe's, 3.32, 3.25; $SiCH(CH_3)_2$, 1.00
3a	DMSO-d_6	4.63	2.46[a]	1.66	4.21	3.83-3.46		7.62	NMe's, 3.31, 3.16
3b	DMSO-d_6	4.60[a]	2.46[a]	1.68	4.20	3.92-3.52		7.58	NMe's, OMe, 3.31, 3.26, 3.16; OCH_2O, 4.58
	$CDCl_3$	4.65[a]	2.58	2.05	4.35	4.03-3.75		7.33	NMe's, OMe, 3.41, 3.38, 3.34; OCH_2O, 4.68
3c	$CDCl_3$	4.72	2.54	1.90	4.30	3.78	4.05	7.32	NMe's, 3.47, 3.30 $SiCH(CH_3)_2$, 1.04
3d	$CDCl_3$	4.68	2.61	2.04	4.35	4.06-3.51		7.27	NMe's, OMe, 3.41, 3.39, 3.35; OCH_2O, 4.77; OCH_2CH_2O, 4.06-3.51

a. Partially obscured

TABLE 3
Selected $^3J_{H,H}$ Coupling Constants (Hz) in 2-Deoxy-C-Nucleosides

Compd.	Solvent	$J_{1',2'\alpha}$	$J_{1',2'\beta}$	$J_{2'\alpha,2'\beta}$	$J_{2'\alpha,3'}$	$J_{2'\beta,3'}$	$J_{3',4'}$
1b	DMSO-d_6	5.9	9.3	12.7	2.4	5.6	2.7
	$CDCl_3$	6.0	8.7	13.3	2.9	6.3	3.5
1c	$CDCl_3$	6.0	9.6	13.2	2.4	6.0	b
1d	$CDCl_3$	6.3	8.8	13.1	3.2	6.2	3.0
2a	DMSO-d_6	6.9	6.8	12.5	5.7	7.0[c]	4.6
2b	DMSO-d_6	7.4	6.8[d]	12.5	6.2	6.7	b
	$CDCl_3$	5.8	8.7	13.8	3.2	6.5	b
2c	$CDCl_3$	5.4	8.7	13.6	2.5	6.2	b
3a	DMSO-d_6	8.3	6.1	13.4	6.0	2.7	b
3b	DMSO-d_6	8.7	5.9	13.5	6.1	2.4	b
	$CDCl_3$	9.8	5.3	13.9	6.0	e	b
3c	$CDCl_3$	8.9	5.5	13.9	5.5	1.7	b
3d	$CDCl_3$	9.7	5.0	14.2	5.9	0.6	b

a. Coupling constants for compound 1a are reported in Table 1.

b. Not analyzed.

c. Based on width (26.3 Hz) of the partially obscured $H_{2'\beta}$-multiplet.

d. Based on width (26.0 Hz) of the partially obscured $H_{2'\beta}$-multiplet.

e. Not observed.

Coupling constants between furanosyl hydrogens in compounds 1b, 1c, and 1d in $CDCl_3$ are similar to those observed for 1a and 1b in DMSO-d_6 (Tables 1 and 3). This indicates that β-D-erythro derivatives 1 preferentially assume S-type conformations, regardless of solvent and $O5'$-substitution.[34,35]

^1H NMR spectra of the α-D-erythro derivative 2b were recorded in $CDCl_3$ and DMSO-d_6 (Tables 2 and 3). In both solvents the chemical shift difference ($\Delta\delta$) between the C_2'-hydrogens (0.70 and 0.67 ppm) is considerably larger than that observed for the β-D-erythro isomer 1b (0.58 and 0.31 ppm). This is consistent with the known shielding exerted by a C_3'-hydroxyl on the cis-C_2' hydrogen;[36] in a β-D-erythro derivative, this effect opposes the deshielding of $H_{2'\alpha}$ by the pyrimidinyl group.

The coupling constants observed for 2b and 2c in $CDCl_3$ (Table 3) are in fair agreement with those reported for α-2'-deoxy-thymidine in D_2O.[37] However, changing solvent to DMSO-d_6 apparently leads to a significant change in preferred conformation(s) of 2; $J_{1',2'\alpha}$ is larger than $J_{1',2'\beta}$ in DMSO-d_6 for 2a and 2b, whereas the opposite trend is observed in $CDCl_3$ for 2b and 2c. Also the $H_{2'}$, $H_{3'}$ coupling constants seem to change considerably with solvent (Table 3).

The β-D-threo derivatives 3 do not show the same sensitivity of conformation to solvent as the α-D-erythro isomers 2; observed furanose-ring coupling constants for 3a, 3b, 3c, and 3d are similar regardless of solvent. Suprisingly, in spectra of 3b and 3c recorded in $CDCl_3$ $\Delta\delta$ for the C_2' hydrogens is of the same magnitude as observed for the β-D-erythro isomers 2b and 2c. However, when using DMSO-d_6 as solvent $\Delta\delta$ for the C_2' hydrogens of 3b is 0.78 ppm which is considerably larger than the $\Delta\delta$ (0.31 ppm) observed for 1b in the same solvent. It is apparent that the preferred conformation of the aglycone of 3b and the associated effects of pyrimidinyl anisotropy changes with solvent.

TABLE 4

^{13}C NMR Chemical Shifts δ (ppm) of 2'-Deoxy-C-Nucleosides

Comp.	Solvent	$C_{1'}$	$C_{2'}$	$C_{3'}$	$C_{4'}$	$C_{5'}$	N_1Me	C_2	N_3Me	C_4	C_5	C_6	Other
1a	DMSO-d_6	73.41	40.80	71.47	87.12	62.09	36.47	151.15	27.31	161.93	112.64	140.48	
1b	DMSO-d_6	73.36[a]	39.77	72.22[a]	84.84	68.16	36.47	151.10	27.26	161.77	112.53	140.21	OMe, 54.61; OCH_2O, 95.90
	$CDCl_3$	73.99[a]	41.52	73.83[a]	84.96	68.31	37.02	151.63	27.76	162.30	114.27	138.89	OMe, 55.36; OCH_2O, 96.69
1c	$CDCl_3$	74.13[a]	41.95	73.86[a]	86.64	64.16	36.91	151.65	27.76	162.27	114.54	138.54	$SiCH(CH_3)_2$, 17.95, 11.89
1d	$CDCl_3$	73.86[a]	40.98	73.15[a]	84.96	68.44	36.97	151.60	27.70	162.22	114.38	138.92	OMe, 58.96; OCH_2O, 95.80; OCH_2CH_2O, 71.75, 66.98
2a	DMSO-d_6	73.09	b	71.57	86.20	61.70	36.36	151.04	27.20	161.83	113.50	140.10	
2b	DMSO-d_6	73.22[a]	40.31	71.84[a]	83.98	67.75	36.41	151.10	27.26	161.85	113.12	140.37	OMe, 54.59; OCH_2O, 95.89
	$CDCl_3$	75.47[a]	40.24	73.98[a]	85.66	68.14	36.97	151.46	27.81	162.60	113.49	140.76	OMe, 55.22; OCH_2O, 96.56
2c	$CDCl_3$	76.02	40.32	74.24	87.40	64.65	36.80	151.38	27.65	162.49	113.95	140.44	$SiCH(CH_3)_2$, 17.79, 11.72
3a	DMSO-d_6	72.55	40.96	70.81	83.49	60.03	36.52	151.05	27.31	162.10	113.12	140.91	
3b	DMSO-d_6	72.87[a]	40.85	70.92[a]	81.59	66.42	36.68	151.05	27.31	162.10	112.85	141.02	OMe, 54.56; OCH_2O, 95.90
	$CDCl_3$	75.59[a]	40.05	72.72[a]	82.47	66.65	37.02	151.38	27.97	162.70	112.27	142.06	OMe, 55.33; OCH_2O, 96.83
3c	$CDCl_3$	74.05[a]	40.87	73.05[a]	82.61	62.40	36.89	151.46	27.76	162.54	113.70	140.44	$SiCH(CH_3)_2$, 17.87, 11.75
3d	$CDCl_3$	75.12[a]	40.11	72.45[a]	82.25	66.44	36.91	151.33	27.86	162.60	112.48	141.74	OMe, 58.85; OCH_2O, 95.69; OCH_2CH_2O, 71.64, 66.92

a. Assignments could be reversed.
b. Obscured by DMSO-d_6.

Comparison of the ^1H NMR spectra of compounds 1-3 reveals that $H_{1'}$ of the β-D-erythro derivatives 1 consistently absorb downfield of $H_{1'}$ in the corresponding diastereomers.

^{13}C NMR spectra of compounds 1-3 were recorded in $CDCl_3$ and/or DMSO-d_6. Assignments are based on analysis of undecoupled spectra recorded with gated decoupling, completely decoupled ^{13}C NMR spectra, and spectra obtained with selective ^{13}C-[^1H] decoupling. Inspection of Table 4 reveals that absorptions due to $C_{4'}$ and $C_{5'}$ seem sensitive to changes in relative stereochemistry. Thus, $C_{4'}$ and $C_{5'}$ of β-D-erythro derivatives 1 absorb upfield of corresponding resonances of stereoisomeric derivatives 2 and 3, when measured in DMSO-d_6 solution. This trend is not evident in spectra taken in $CDCl_3$ solutions.

In conclusion, each of the three stereoisomeric configurations discussed herein seems to be identifiable by ^1H and ^{13}C NMR spectrometry using a combination of characteristic coupling constant and chemical shift criteria. This should be helpful in the assignment of relative stereochemistries of new 2'-deoxy-C-nucleosides.

EXPERIMENTAL SECTION

The syntheses of compounds 1-3 have been reported[16,17] or will be described elsewhere.[19]

^1H and ^{13}C NMR spectra were obtained on a JEOL FX Q spectrometer at 90 MHz and 22.5 MHz, respectively, and were referenced to tetramethylsilane. Coupling constants were refined by use of a JEOL FASNO 5 NMR spectrum simulation program.

ACKNOWLEDGEMENT

Financial support of this work from the National Institute of General Medical Science (Grant GM 30310), from the American Cancer Society, from S. Söderlunds Minnesfond and from Thuns fond is greatly appreciated.

REFERENCES AND FOOTNOTES

1. For recent reviews of the biology and chemistry of C-nucleosides, see U. Hacksell, and G. D. Daves Jr., Prog. Med. Chem., in press; G. D. Daves Jr., and C. C. Cheng, Ibid., 13, 303 (1976); S. Hanessian, and A. G. Pernet, Adv. Carbohydr. Chem. Biochem., 33, 111 (1976); J. J. Fox, K. A. Watanabe, R. S. Klein, C. K. Chu, S. Y. K. Tam, U. Reichman, K. Hirota, I. Wempen, C. Lopez, and J. H. Burchenal, INSERM. Colloq., 81, 241 (1978).

2. T. C. Jain, A. F. Russell, and J. G. Moffatt, J. Org. Chem., 38, 3179 (1973).

5. S. D. Bridges, D. M. Brown, and R. C. Ogden, J. Chem. Soc.,

10. A. Matsuda, K. Pankiewicz, B. K. Marcus, K. A. Watanabe, and J. J. Fox, Carbohydr. Res., 100, 297 (1982).

11. For an excellent review, see D. B. Davies, Prog. Nucl. Magn. Reson. Spectrosc., 12, 135 (1978).

12. I. Arai, and G. D. Daves Jr., J. Org. Chem., 43, 4110 (1978).

14. I. Arai, T. D. Lee, R. Hanna, and G. D. Daves Jr., Organometallics, 1, 742 (1982).

15. T. D. Lee, and G. D. Daves Jr., J. Org. Chem., 48, 399 (1983).

16. U. Hacksell, and G. D. Daves Jr., Organometallics, 2, 772 (1983).

18. Idem, Ibid., 48, 4144 (1983).

19. J. C.-Y. Cheng, U. Hacksell, and G. D. Daves Jr., J. Org. Chem., (1986), in press.

20. H. T. Kalinoski, U. Hacksell, D. F. Barofsky, E. Barofsky, and G. D. Daves Jr., J. Am. Chem. Soc., 107, 6476 (1985).

21. U. Hacksell, H. T. Kalinoski, D. F. Barofsky, and G. D. Daves, Jr., Acta Chem. Scand., B39, 469 (1985).

22. Theoretically, a furanose ring can assume 20 different envelope and twist conformations, see M. Smith, and C. D. Jardetzky, J. Mol. Spectrosc., 28, 70 (1968).

23. C. Altona, and M. Sundaralingam, J. Am. Chem. Soc., 94, 8205 (1972).

24. Idem Ibid., 95, 2333 (1973).

25. E. Westhof, and M. Sundaralingam, Ibid., 105, 970 (1983).

26. N denotes a pesuedorotational interval (P=0±90°) containing the C_3' endo and C_2' exo conformations. S stands for P=180±90° and contains the C_2' endo and C_3' exo conformers, see Ref. 23.

27. J. Wiorkiewicz-Kuczera, and A. Rabzenko, J. Chem. Soc., Perkin Trans. II, 789 (1985).

28. F. A. A. M. de Leeuw, C. Altona, H. Kessler, W. Bermel, A. Friedrich, G. Krack, and W. E. Hull, J. Am. Chem. Soc., 105, 2237 (1983).

29. F. A. A. M. de Leeuw, and C. Altona, J. Chem. Soc., Perkin Trans. II, 375 (1982).

30. M. J. Robins, M. MacCoss, and J. S. Wilson, J. Am. Chem. Soc., 99, 4660 (1977).

31. A. A. Grey, I. C. P. Smith, and F. E. Hruska, J. Am. Chem. Soc., 93, 1765 (1971).

32. B. Fraser-Reid, and B. Radatus, J. Am. Chem. Soc., 93, 6342 (1971).

33. K. N. Slessor, and A. S. Tracey, Carbohydr. Res., 27, 407 (1973).

34. Reanalysis of the ^1H NMR spectrum of 1,3-dimethyl-2'-deoxy-5'-O-tritylpseudouridine[6] (kindly provided by Dr. Kyoichi A. Watanabe), revealed that $J_{3',4'}$ is 3.3 Hz (confirmed by spin-spin simulation), and not 7.6 Hz as previously reported.[6] This allows reassignment $H_{2'}$ and $H_{2''}$ and indicates that also this compound (and its N_1-monomethylated analogue[6]) exists mainly in the S-conformation in $CDCl_3$.

35. For solvent and temperature effects in NMR spectra of N-nucleosides, see ref. 33, and T. Schleich, B. J. Blackburn, R. D. Lapper, and I. C. P. Smith, Biochemistry, 11, 137 (1972); S. Tran-Dinh, J.-M. Neumann, J.-M. Thiery, T. Huynh-Dinh, J. Igolen, and W. Guschlbauer, J. Am. Chem. Soc., 99, 3267 (1977); M. P. Schweizer, E. B. Banta, J. T. Witkowski, and R. K. Robins, Ibid., 95, 3770 (1973).

36. K. N. Fang, N. S. Kondo, P. S. Miller, and P. O. P. Ts'O, J. Am. Chem. Soc., 93, 6647 (1971).

37. R. U. Lemieux, Can. J. Chem., 39, 116 (1961).