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THE CARBINYL ACETYLATION SHIFTS:
A POTENTIAL TOOL FOR DIFFERENTIATING THE CONFORMATIONS OF SECONDARY ALLYLIC ALCOHOLS ON SIX-MEMBERED RINGS

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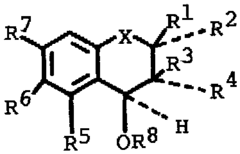
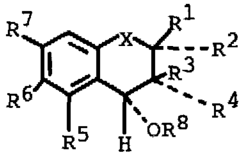
Acetylation shifts in ^{1}H-NMR spectroscopy have played an important role in organic chemistry since they were originally introduced, by Kawazoe and his coworkers, as a diagnosis for the relative spatial relationship between the ring methyls and hydroxyls in steroids and related compounds.[1] With regard to assignment of the hydroxyl conformation itself, however, their studies of carbinyl acetylation shifts terminated in ambiguous results.[2] Possible conformational dependency of the shifts for carbinyl protons mentioned by Tori and Komeno is not intended for practical use owing to the limited accumulation of data.[3] This paper describes a new practical method for determining the conformation of hydroxyls in tetralol analogs by use of acetylation shifts for benzylic carbinyl protons.[4]

Table I lists chemical shifts for benzylic methine protons in tetralol analogs. As seen, the acetylation shifts (ΔAc) are always larger for quasi-axial alcohols (ΔAc_{ax}) than for quasi-equatorial counterparts (ΔAc_{eq}). The difference between ΔAc_{ax} and ΔAc_{eq} is increased when the solvent is changed to more polar one such as DMSO. The order of their magnitude ($\Delta Ac_{ax} > \Delta Ac_{eq}$) is regular in allylic secondary alcohols on six-membered rings. This empirical rule can be utilized to assign the conformation of 1-tetralol and 4-chromanol analogs. Especially, the value (ΔAc in $CDCl_3$ solution) higher than 1.24 ppm corresponds to the quasi-axial benzylic hydroxyl in flavanols, and that lower than 1.20 ppm to the quasi-equatorial one. The rule also finds a favorable application to the stereochemical assignment of 1-tetralols bearing no vicinal proton on C_2, such as 2,2-dimethyl-3-phenyl- and 2,2,3-trimethyl-1-tetralol. The assignment of their hydroxyl conformations based on the deshielding effect of the C_1-quasi-equatorial hydroxyl upon the C_8-aromatic proton is consistent with that from the present rule.

As seen in Table I, in epimeric pairs of tetralol analogs with no adjacent groups having any significant anisotropic shielding effect, the axial carbinyl protons resonate downfield from their equatorial counterparts. This order of the chemical shifts is reverse to the usual order[5] found in the resonance of

Table I : Chemical shifts (δ in $CDCl_3$) for benzylic methine (carbinyl) protons and ΔAc values.[13]





R^1	R^2	R^3	R^4	R^5	R^6	R^7	X	R^8 H	R^8 Ac	ΔAc_{eq}	R^8 H	R^8 Ac	ΔAc_{ax}	
Ph	H	H	H	H	H	H	O	5.02	6.18	1.16	4.78	6.04	1.26	a,b
Me	H	H	H	H	H	H	O	4.78	5.95^c	1.17	4.62	5.84^c	1.22	a,d
Et	H	H	H	H	H	H	O	4.87	6.07	1.20	4.72	5.98	1.26	d
4-MeO-Ph-	H	H	H	H	H	Me	O	-	-	-	4.77	6.01	1.24	a,e
Me-CH=CH-	H	H	H	H	Me	H	O	4.86	6.03	1.17	-	-	-	a,f
4-MeO-Ph-	H	H	H	H	H	OMe	O	-	-	-	4.78	6.03	1.25	a,g
3,4-$(MeO)_2$Ph-	H	H	H	H	H	H	O	(C_8-OMe)	-	-	4.80	6.04	1.24	a,g
4-MeO-Ph-	H	H	H	H	H	H	O	-	-	-	4.78	6.03	1.25	a,h
Me(OCH_2CH_2O)C-	OH	H	H	H	H	H	CH_2	4.95	6.19	1.24	4.80	6.18	1.38	
Me(SCH_2CH_2S)C-	OH	H	H	H	H	H	CH_2	5.00	6.20	1.20	4.83	6.21	1.38	
Ph	H	H	H	H	H	H	CH_2	4.95	6.20	1.25	4.90	6.19	1.29	i,j
Me	H	H	H	H	H	H	CH_2	4.78	6.03	1.25	4.77	6.04	1.27	i,j
								4.64	5.91	1.27	4.59	5.91	1.32	k
Ac	OR^8*	H	H	H	H	H	CH_2	5.05	6.15	1.10	4.88	6.18	1.30	
Et	H	H	H	OMe	H	H	CH_2	5.05	6.24	1.19	5.07	6.28	1.21	l
H	H	H	Me	H	H	H	CH_2	4.30	5.78	1.48	4.54	6.03	1.49	j,m
								4.14	5.62	1.48	4.35	5.88	1.53	k
Ph	H	Me	Me	H	H	H	CH_2	4.55	6.05	1.50	4.25	5.78	1.53	
								4.38	5.90	1.52	4.07	5.64	1.57	k
Me	H	Me	Me	H	H	H	CH_2	4.34	5.86	1.52	4.18	5.72	1.54	
								4.18	5.71	1.53	3.99	5.59	1.60	k
podophyllotoxin and the C_1-epimer								4.86	5.80	0.94	4.75	6.05	1.30	n
2,3-dimethyl-5-phenyl-2-cyclohexenol								4.30	5.54	1.24	4.08	5.35	1.27	
5-phenyl-2-cyclohexenol								4.45	$-^o$	-	4.29	$-^o$	-	p

a) Data in the literature. b) J. W. Clark-Lewis, Aust. J. Chem., **21**, 2059 (1968).
c) Values in CCl_4 solution. d) K. Hanaya and K. Furuse, Nippon Kagaku Zasshi, **89**, 1002 (1968). e) J. W. Clark-Lewis and E. J. McGarry, Aust. J. Chem., **26**, 809 (1973).
f) C. Tamm, B. Böhner and W. Zürcher, Helv. Chim. Acta, **55**, 510 (1972).
g) J. W. Clark-Lewis and E. J. McGarry, Aust. J. Chem., **26**, 2447 (1973).
h) J. W. Clark-Lewis and M. I. Baig, ibid., **24**, 2581 (1971).
i) K. Hanaya, Nippon Kagaku Zasshi, **87**, 995 (1966). j) Different data were reported for these compounds; see S. Mitsui, A. Kasahara and K. Hanaya, Bull. Chem. Soc. Japan, **41**, 2526 (1968). k) Values in DMSO-d_6 solution. l) Z. Horii, T. Momose and Y. Tamura, Chem. Pharm. Bull., **13**, 737 (1965). m) K. Hanaya, Nippon Kagaku Zasshi, **87**, 991 (1966). n) D. C. Ayres, J. A. Harris, P. N. Jenkins and L. Phillips, J. Chem. Soc. Perkin I, 1343 (1972). o) Undeterminable owing to overlapping of signals with olefinic protons.
p) K. Hanaya, Nippon Kagaku Zasshi, **91**, 82 (1970).
*) Only the diacetate was formed on acetylation.

the epimeric carbinyl protons in cyclohexanols. The reversed order of chemical shifts has been reported for the protons at the α-ketonic and vinylogous α-ketonic position,[6] but it is not characteristic of those adjacent to the sp^2 system as evidenced in the resonance of benzylic protons in simple tetralones.[7] The difference in chemical shift between epimeric carbinyl protons in tetralol analogs is decreased on acetylation. One of the possible explanations for the inversion in the present system may be found in those associated with the spatial orientation of the hydroxyl[8] and deshielding effect of the hydroxyl oxygen lone pairs.[9] The quasi-equatorial alcohols have more probabilities of anti conformation,[8,10] where the carbinyl proton is skew to two electron pairs of the hydroxyl oxygen, than do the quasi-axial ones, and hence the carbinyl protons in the former may resonate at the lower field. In acetates, the difference in effect of the electron pairs on each carbinyl proton and consequently in chemical shift between both protons may be decreased.[11] Consequently, ΔAc_{ax} should be always higher than ΔAc_{eq}. The relative chemical shift for the carbinyl protons in an epimeric pair of 3-ethyl-8-methoxy- or 2-methyl-1-tetralol is reversed[12] exceptionally. The ΔAc_{ax}, however, is higher than the ΔAc_{eq}, and the rule holds still good. To our knowledge, no exception to this rule is found except for compounds with any factors to vary the usual spatial orientation of the hydroxyls as in 1-tetralols of α-glycol types.

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NOTES AND REFERENCES

1. Y. Kawazoe, Y. Sato, M. Natsume, H. Hasegawa, T. Okamoto and K. Tsuda, Chem. Pharm. Bull., **10**, 338 (1962); T. Okamoto and Y. Kawazoe, ibid., **11**, 643 (1963).
2. Y. Kawazoe, Y. Sato, T. Okamoto and K. Tsuda, ibid., **11**, 328 (1963).
3. A preferred deshielding of axial carbinyl protons (in equatorial alcohols) on acetylation has been reported in a few examples of steroidal alcohols or thiols; see K. Tori and T. Komeno, Tetrahedron, **21**, 309 (1965).
4. A part of this work was presented at the 18th Symposium on the Chemistry of Natural Products, Kyoto, October, 1974, where we used the abbreviated symbols of ΔAc_{ax} and ΔAc_{eq} conversely for the acetylation shifts of the quasi-axial carbinyl protons in quasi-equatorial alcohols and those of the quasi-equatorial ones in the epimers, respectively. The present ones are less confusing.
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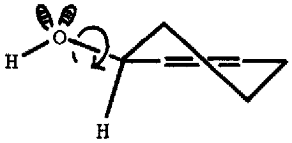
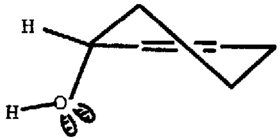
6. See, for example, D. J. Collins, J. J. Hobbs and S. Sternhell, Tetrahedron Letters, 197 (1963); K. Tori and K. Kuriyama, ibid., 3939 (1964); Idem, Chem. Ind. (London), 1525 (1963).

7. Cf. Z. Horii, T. Momose and Y. Tamura, Chem. Pharm. Bull., 13, 651 (1965).

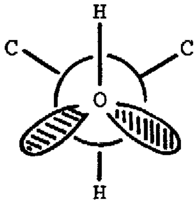
8. The alcohols have conformations I, II and III resulting from rotation about the C-O bond. See M. Ōki and H. Iwamura, Bull. Chem. Soc. Japan, 32, 950 (1959).



quasi-equatorial alcohol

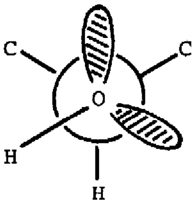


quasi-axial alcohol



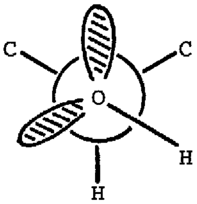
anti

(I)



gauche

(II)



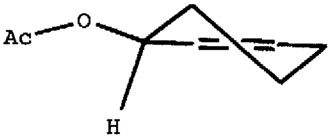
gauche

(III)

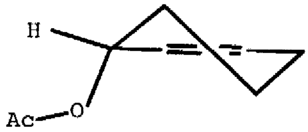
9. Price mentioned the contribution of lone pair electrons on oxygen or nitrogen to the ^{1}H-NMR deshielding of the α-protons in ethers or amines [C. C. Price, J. Org. Chem., 38, 615 (1973)].

10. Aaron and his co-workers suggested the outside orientation of the O-H bond in axial cyclohexanols. H. S. Aaron, C. P. Ferguson and C. P. Rader, J. Am. Chem. Soc., 89, 1431 (1967); C. P. Rader, J. Am. Chem. Soc., 88, 1713 (1966); J. J. Uebel and H. W. Goodwin, J. Org. Chem., 31, 2040 (1966).

11. The oxygen lone pair electrons are delocalized and the conformation is almost fixed as depicted below.



quasi-equatorial



quasi-axial

12. The effect derived from the hydroxyl orientation is probably surpassed in magnitude by a shielding or deshielding effect of the C_2-Me bond or the OMe.

13. ^{1}H-NMR spectra were measured with a R-22 Hitachi high resolution NMR spectrometer operating at 90 MHz in $CDCl_3$ or DMSO-d_6 with TMS as an internal standard; δ ±0.01 ppm.