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Magnesium-Induced Shifts in the Proton Magnetic Resonance Spectra of Phenols

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It was observed that in numerous phenols the phenolic hydroxyl and *ortho* proton resonances in the proton nuclear magnetic resonance (^{1}H NMR) spectrum moved downfield on addition of anhydrous magnesium chloride to the dimethyl sulfoxide-d_6 or dimethylformamide-d_7 solution. The selective shifts of phenolic *ortho* proton resonances in the presence of magnesium chloride were shown to be a useful tool for ^{1}H NMR signal assignments and structure elucidation of naturally occurring phenols.

Keywords——^{1}H NMR; magnesium chloride; phenol; shift reagent; flavonoid; dimethyl sulfoxide-d_6; dimethylformamide-d_7

In the previous paper[1] we reported that the phenolic hydroxyl and *ortho* proton resonances in proton nuclear magnetic resonance (^{1}H NMR) spectra showed downfield shifts on addition of alkaline earth salts to phenols in dimethyl sulfoxide-d_6 (DMSO-d_6), and among the alkaline earth salts, anhydrous magnesium chloride caused the strongest downfield shifts, for both the phenolic hydroxyl and *ortho* protons. It was suggested that magnesium chloride might be applied as a shift reagent to the structure elucidation of natural phenols because of this selective shift of the phenolic *ortho* proton resonances. This paper describes our observations of the selective shift due to anhydrous magnesium chloride in the ^{1}H NMR spectra of various phenols and some applications of the magnesium chloride shifts to structure elucidation of natural phenols.

Experimental

Materials——Kaempferol and quercetin from a horticultural species of rose, Cl. Peace BRADY, and demethylhomolycorine and 4′-hydroxy-7-methoxyflavan from *Lycoris radiata* HERB. were used for the present experiments. All the other chemicals were obtained from Tokyo Kasei Kogyo Co., Ltd., Wako Pure Chemical Industries Ltd. and Aldrich Chemical Co.

NMR Measurements——^{1}H NMR spectra were recorded on a Hitachi R-40 spectrometer at 90 MHz in DMSO-d_6 with tetramethylsilane (TMS) as an internal reference in 5 mm spinning tubes at 37 °C. The amount of phenols used was 0.3 mol, and a 1.5 mol ratio of magnesium chloride was added to the phenols.

Results and Discussion

The effects of anhydrous magnesium chloride on the aromatic proton resonances in the ^{1}H NMR spectra of various phenols were examined according to the procedure described in Experimental. Table I shows that in most of the phenols the signals of the phenolic hydroxyl and *ortho* proton moved downfield on addition of anhydrous magnesium chloride, and the magnitude of the shift of the *ortho* proton was from 0.06 to 0.28 ppm. Exceptionally, the

TABLE I. The $MgCl_2$-Induced Shifts in the ^1H NMR Spectra of Various Phenols

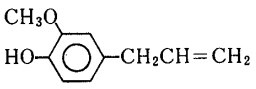
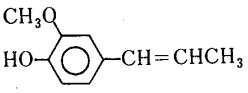
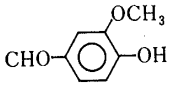
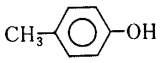
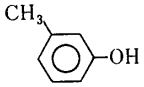
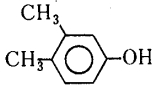
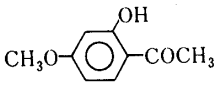
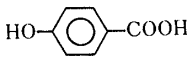
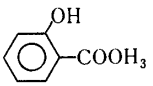
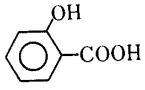
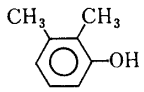
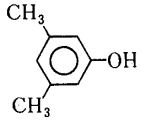
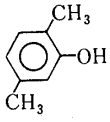
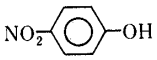
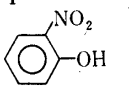
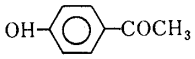
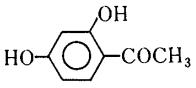
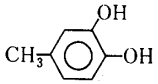
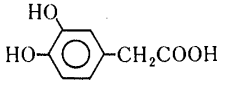
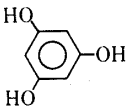
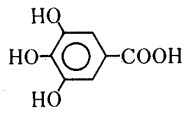
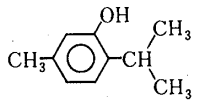
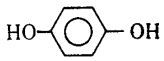
Compound	Proton	Shift (ppm)[a]
Eugenol 	*o*[b]-H	+0.16 (+0.23)[e]
	m[b]-H(3)[c]	0 (−0.02)
	m-H(5)	0 (−0.01)
	OMe	0 (0)
	allyl	0 (0)
	OH	+0.50 (—)
Isoeugenol 	*o*-H(6)	+0.15
	m-H(3)	0
	m-H(5)	−0.03
	OMe	0
	allyl	0
	OH	—
Vanillin 	*o*-H	+0.25
	m-H(2, 6)	0
	OMe	−0.01
	CHO	+0.01
	OH	—
p-Cresol 	*o*-H	+0.11
	m-H	0
	Me	0
	OH	+0.55
m-Cresol 	*o*-H(2)	+0.11
	o-H(6)	+0.09
	m-H	0
	p[b]-H	0
	Me	0
	OH	+0.59
o-Xylenol 	*o*-H(2)	+0.10
	o-H(6)	+0.10
	m-H	−0.02
	Me	0
	OH	+0.52
2-Hydroxy-4-methoxy-acetophenone 	*o*-H	+0.10
	m-H	+0.01
	p-H	0
	Ac	0
	OMe	0
	OH	−0.09
p-Hydroxybenzoic acid 	*o*-H	+0.14
	m-H	−0.03
	COOH	—
	OH	—
Methyl salicylate 	*o*-H	+0.11
	m-H(4)	−0.02
	m-H(6)	−0.03
	p-H	−0.02
	Me	−0.02
	OH	+0.17
Salicylic acid 	*o*-H	+0.02
	m-H(4)	0
	m-H(6)	0
	p-H	0
	COOH	—
	OH	—
2,3-dimethylphenol 	*o*-H	+0.20
	m-H	+0.02
	p-H	0
	Me	0
	OH	+0.52
3,5-Dimethylphenol 	*o*-H	+0.11
	p-H	0
	Me	0
	OH	+0.56
2,5-Dimethylphenol 	*o*-H	+0.22
	m-H	−0.01
	p-H	−0.01
	Me	0
	OH	+0.56
p-Nitrophenol 	*o*-H	+0.14
	m-H	−0.02
	OH	—
o-Nitrophenol 	*o*-H	+0.28
	m-H(3)	−0.05
	m-H(5)	−0.03
	p-H	−0.08
	OH	—
p-Hydroxyacetophenone 	*o*-H	+0.12
	m-H	−0.01
	Ac	0
	OH	—
2,4-Dihydroxyaceto-phenone 	*o*-H(3)	+0.22
	o(*p*)[d]-H(5)	+0.14
	m-H	−0.01
	Ac	0
	OH(2)	−0.01
	OH(4)	+0.75
Homocatechol 	*o*(*m*)-H(3)	+0.08
	o(*m*)-H(6)	+0.08
	m(*p*)-H(5)	−0.01
	Me	−0.01
	OH	+0.38
3,4-Dihydroxyphenyl-acetic acid 	*o*(*m*)-H(2)	+0.06
	o(*m*)-H(5)	+0.06
	m(*p*)-H(6)	0
	CH_2	0
	COOH	—
	OH	—
Phloroglucinol 	*o*-H	+0.11
	OH	+0.26
Gallic acid 	*o*-H	+0.06
	COOH	—
	OH	+0.25

TABLE I. (continued)

Compound	Proton	Shift (ppm)[a]	Compound	Proton	Shift (ppm)
Thymol 	*o*-H	+0.24			
	m-H	−0.02			
	p-H	−0.03			
	Me	0			
	OH	+0.57			
Hydroquinone 	*o*-H	+0.06			
	OH	+0.42			

a) Plus sign denotes a downfield shift.
b) The position of the proton with respect to the hydroxyl group.
c) The proton number.
d) Indicating a proton *ortho* to one hydroxyl group and *para* to another.
e) Measured in DMF-d_7.

magnitude of the shift in salicylic acid, one of the compounds forming intramolecular hydrogen bonds, was small or negligible. Some variation of splitting pattern due to the downfield shift was observed in the spectra of some phenols.

On the other hand, in the same experiment on two alcohols, 3-phenyl-1-propanol and 1-phenylethanol, the alcoholic hydroxyl proton resonances showed downfield shifts (+0.33 and +0.39 ppm, respectively), whereas the alcohol β-protons, corresponding to the phenolic *ortho* protons, and other protons did not. Thus, the downfield shift due to magnesium chloride was proved to be selective to phenolic *ortho* protons except for hydroxyl ones. This shift was also observed in the experiment using dimethylformamide-d_7 (DMF-d_7) instead of DMSO-d_6 as a solvent (*cf.* eugenol in Table I). However, it was not observed in other solvents.

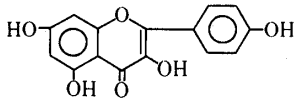
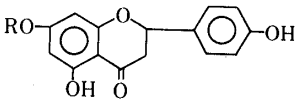
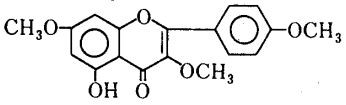
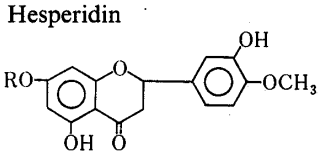
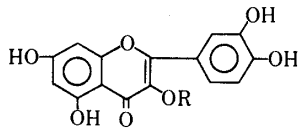
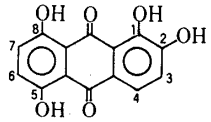
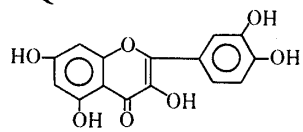
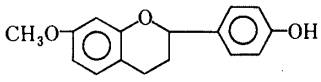
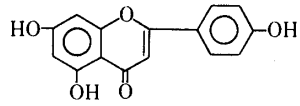
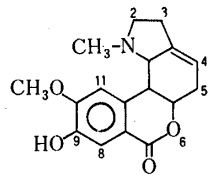
Next, some flavonoids and an anthraquinone were studied. As shown in Table II, the spectra of kaempferol, rutin and apigenin showed downfield shifts of all the phenolic *ortho* proton resonances on addition of magnesium chloride. However, the spectra of naringin, hesperidin and quinalizarin did not show downfield shifts of the protons *ortho* to hydroxyl groups which could form strong intramolecular hydrogen bonds to ketone, although all the other phenolic *ortho* proton resonances moved downfield. This result was supported by the measurement on kaempferol 3,4′,7-trimethyl ether, all the protons of which showed no shift.

On the other hand, it was found that in quercetin the signal of the proton *ortho* to the 3′-hydroxyl group among the phenolic *ortho* protons was almost unaffected by magnesium chloride. This abnormal behavior of the flavonol bearing a 3′-hydroxyl group might be associated with the presence of the free 3-hydroxyl group, because the spectrum of rutin bearing rutinose on the 3-hydroxyl group showed a normal shift.

The structures of the aromatic parts of the known compounds, 4′-hydroxy-7-methoxyflavan and demethylhomolycorine, obtained from *L. radiata* were easily elucidated by the application of the $MgCl_2$-induced shift. Also, the structure of a new compound, 3′,7-dihydroxy-4′-methoxy-8-methylflavan, isolated from the same plant, was established by the application of magnesium chloride as a shift reagent.[2)]

The well-known shift reagents, $Eu(DPM)_3$ *etc.*, are not suitable for phenols since they decompose slowly in the presence of a phenolic hydroxyl group.[3)] Therefore, the above-mentioned selective shift of phenolic *ortho* protons due to magnesium chloride seems to be a useful tool for ^1H NMR signal assignments and structure elucidation of naturally occurring phenols, even if there are a few exceptional cases.

TABLE II. The $MgCl_2$-Induced Shifts in the ^1H NMR Spectra of Flavonoids and Other Compounds

Compound	Proton	Shift (ppm)[a]	Compound	Proton	Shift (ppm)
Kaempferol 	*o*[b]-H(6)[c]	+0.17	Naringin 	*o*-H(6)	0
	o(*p*)[d]-H(8)	+0.19		*o*-H(3′,5′)	+0.08
	o-H(3′,5′)	+0.14		*m*-H(2′,6′)	0
	m[b]-H(2′,6′)	0		*p*[b]-H(8)	0
	OH	—		OH(5)	0
Kaempferol 3,4′,7-trimethyl ether 	*o*-H(6)	0	R=rhamnoglucosyl	OH(4′)	+0.30
	8-H	0	Hesperidin 	*o*-H(6)	0
	2′,6′-H	0		*o*-H(2′)	+0.14
	3′,5′-H	0		*m*-H(5′)	0
	OH	—		*p*-H(8)	0
Rutin 	*o*-H(6)	+0.16		*p*-H(6′)	0
	o(*p*)-H(8)	+0.20	R=rutinosyl	OMe	—
	o(*m*)-H(2′)	+0.08		OH(5)	0
	o(*m*)-H(5′)	+0.14		OH(3′)	+0.39
	m(*p*)-H(6′)	0			
	OH	—	Quinalizarin 	*o*(*m*)-H(3)	+0.30
R=rutinosyl				*o*(*m*)-H(6)	−0.07
Quercetin 	*o*-H(6)	+0.14		*o*(*m*)-H(7)	−0.07
	o(*p*)-H(8)	+0.19		*m*(*p*)-H(4)	−0.12
	o(*m*)-H(2′)	+0.01		OH	—
	o(*m*)-H(5′)	+0.09	4′-Hydroxy-7-methoxyflavan 	*o*-H(3′,5′)	+0.10
	m(*p*)-H(6′)	+0.01		*m*-H(2′,6′)	+0.01
	OH(5)	0		5-H	+0.02
	OH(3,3′,4′,7)	—		6-H	+0.01
Apigenin 	*o*-H(6)	+0.19		8-H	+0.02
	o(*p*)-H(8)	+0.16		OH	+0.44
	o-H(3′,5′)	+0.15	Demethylhomolycorine 	*o*-H(8)	+0.18
	m-H(2′,6′)	+0.03		*m*-H(11)	+0.04
	3-H	+0.03		OH	—
	OH	—			

a) Plus sign denotes a downfield shift.
b) The position of the proton with respect to the hydroxyl group.
c) The proton number.
d) Indicating a proton *ortho* to one hydroxyl group and *para* to another.

References and Notes

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