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# DEPROTONATION INDUCED 13 C NMR SHIFTS IN PHENOLS AND FLAVONOIDS

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Abstract. $^{13}$C-NMR shift changes associated with deprotonation are measured for 15 phenols and 4 flavonoids, leading to several corrections of literature reports. The additive shifts are useful for OH-group acidity determinations and $^{13}$C signal assignments.

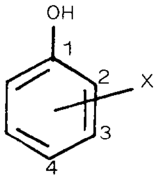
The shielding variation associated with proton abstraction in phenols is of general interest with respect to the electron density distribution in these systems as well as for structure elucidation and $^{13}$C-NMR signal assignments in polyphenolic compounds. A recent publication on phenol deprotonation shifts[1] prompts us to report some measurements which, in agreement with earlier investigations[2] show deshielding at higher $p_H$ for the ipso and the ortho, and larger shielding only for the para carbon atom. Consequently, the direction of $^{13}$C shifts are not consistent[1] with MO calculated electron densities[2b]. The erroneous shifts for phenol in the recent study[1] are not due to concentration or solvent effects[3].

In substituted phenols as well as in naphthols sign and magnitude of the deprotonation induced shifts (DIS) are generally preserved, although acyl substituents in the ortho or para position show the expected mesomeric effects (Table 1). Polyvalent phenols again are characterized by slightly modified DIS values; only the shifts observed for the phloroglucinol anion clearly demonstrate dominating ketone-like structures[4].

In flavonoids or other polyhydroxybenzenes the $^{13}$C-NMR titration curves can be used to follow stepwise deprotonation, corresponding to the different $pK_A$ values[5] of the phenolic groups (e.g.Fig.1). The consecutive deprotonation as contained in table 2 support the acidity sequence 7-OH > 4'-OH > 5-OH which is the basis of several UV methods in the structure analysis of flavonoids[6]. An exception is morin (D)[7], where 2'-OH is ionized first. Deprotonation shifts are also a convenient method for the unambiguous assignment of $^{13}$C-NMR signals.

Table 1. Deprotonation Induced $^{13}$C-NMR Shifts in Phenols[a]

| | X | C1 | C2 | C3 | C4 | C5 | C6 | Other | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | H | 9.94 | 3.64 | -0.32 | -5.98 | -0.32 | 3.64 | | | | |
| 2 | 2=Me | 10.46 | 2.14 | -1.36 | -6.24 | 0.06 | 3.38 | Me 2.08 | | | |
| 3 | 3=Me | 9.88 | 3.51 | -1.04 | -5.72 | -0.39 | 3.57 | -0.32 | | | |
| 4 | 4=Me | 9.62 | 3.38 | -0.19 | -6.50 | -0.19 | 3.38 | 0.00 | | | |
| 5 | 4=OMe | 10.21 | 2.54 | 0.20 | -4.09 | 0.20 | 2.54 | OMe 0.62 | | | |
| | | | | | | | | C7 | C8 | C9 | C10 |
| 6 | ∝-Naphthol | 10.34 | 2.31 | 1.76 | -6.12 | -0.96 | 0.00 | -2.04 | 2.18 | 5.73 | 0.82 |
| 7 | ß-Naphthol | 1.12 | 9.01 | 5.22 | -0.91 | -0.28 | -2.73 | -1.05 | -1.05 | 1.33 | -2.09 |
| | | | | | | | | Me | CO – Me | | |
| 8 | 3=Me,4=COMe | 13.01 | 4.17 | 0.66 | -6.44 | 1.51 | 3.92 | 0.00 | -1.50 | 0.00 | |
| 9 | 2=Me,4=COMe | 13.91 | 2.34 | 0.07 | -6.69 | 1.30 | 3.83 | 0.83 | -0.97 | -0.94 | |
| 10 | 2=COMe,4=Me | 10.20 | 6.56 | -0.72 | -7.74 | -1.63 | 6.37 | 0.00 | -1.63 | 3.56 | |
| 11 | 2=OH | 13.45 | 13.45 | 1.88 | -4.68 | -4.68 | 1.88 | | | | |
| 12 | 3=OH | 10.01 | 6.17 | 10.01 | -0.84 | -1.10 | -0.84 | | | | |
| 13 | 4=OH | 5.33 | 2.53 | 2.53 | 5.33 | 2.53 | 2.53 | | | | |
| 14[b] | 2=OH,3=OH | 8.71 | 5.52 | 8.71 | -1.06 | -0.97 | -1.06 | | | | |
| 15[b] | 3=OH,5=OH | 36.66 | 4.22 | 26.06 | 4.22 | 26.06 | 4.22 | | | | |



a) 2±0.5 M Solutions in $D_2O$/MeOH (20:80) at 300±5 K; DIS (ppm) after addition of 50-100% molar excess NaOH; b) see note 4.

Fig.1. $^{13}$C-NMR Titration Curve of Naringenin (C; see Table 2)

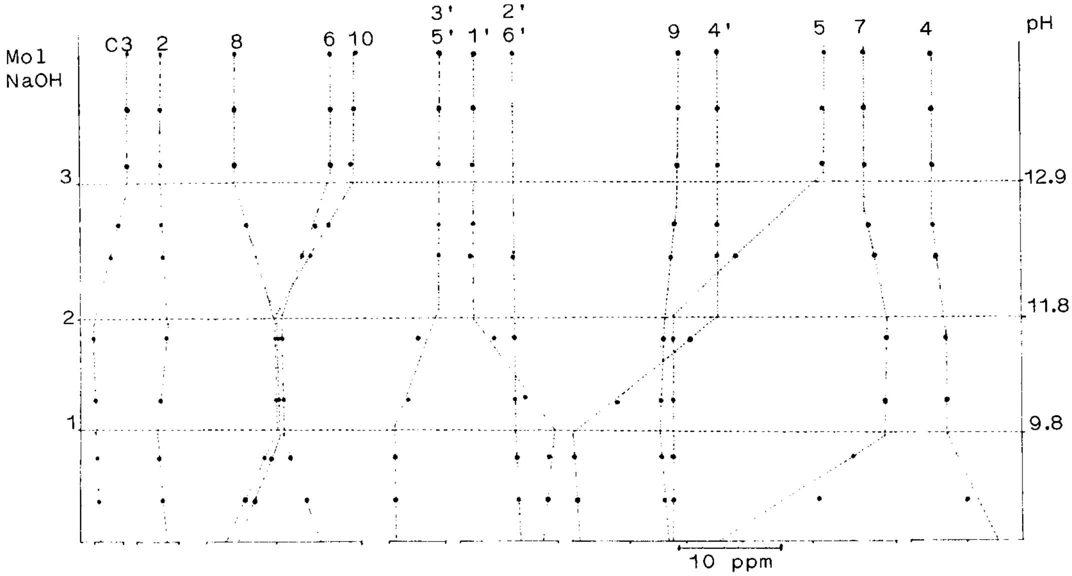


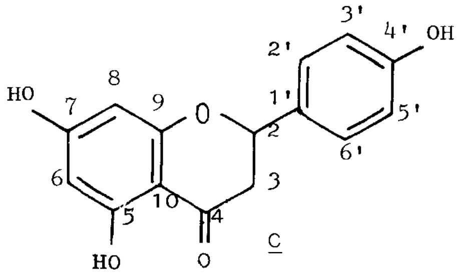
Table 2. Deprotonation Induced $^{13}C$ NMR Shifts in Flavonoids[a]

| | Chrysin A | | | Apigenin B | | | | Naringenin C | | | | Morin D[6] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 5,7(OH)$_2$ Flavone[b] | | | 5,7,4'(OH)$_3$Flavone[b] | | | | 5,7,4'(OH)$_3$Flavanone[c] | | | | 3,5,7,2',4'(OH)$_5$[b] Flavone | |
| $O^-$ in pos. → | | 7 | 5,7 | – | 7 | 7,4' | 5,7,4' | – | 7 | 7,4' | 5,7,4' | – | 2' |
| 2 | 163.46 | -1.56 | -3.90 | 164.24 | 0.33 | 0.13 | -3.25 | 80.27 | -0.46 | 0.39 | -0.52 | 148.97 | 1.17 |
| 3 | 105.29 | -0.58 | 2.21 | 103.15 | -3.06 | 0.59 | 1.23 | 43.55 | -0.46 | 0.06 | 2.35 | 136.23 | 3.05 |
| 4 | 181.99 | -2.28 | -1.04 | 181.99 | -1.04 | -0.13 | -0.78 | 198.17 | -1.57 | -2.14 | -2.08 | 176.27 | 2.07 |
| 5 | 161.38 | -0.20 | 12.10 | 161.51 | -0.45 | 1.88 | 9.82 | 165.15 | -0.14 | 0.34 | 10.20 | 156.96 | 0.46 |
| 6 | 99.18 | 4.42 | 3.32 | 99.12 | 4.42 | 0.52 | 2.47 | 97.30 | 3.25 | -0.33 | 5.52 | 93.53 | 0.45 |
| 7 | 164.44 | 14.17 | 1.96 | 163.91 | 13.83 | -0.22 | -1.77 | 168.27 | 13.00 | 0.33 | -2.80 | 163.79 | -0.39 |
| 8 | 94.37 | 4.42 | -5.33 | 94.37 | 3.12 | -0.52 | -3.04 | 96.45 | 3.70 | -0.19 | -3.05 | 98.21 | 0.06 |
| 9 | 157.81 | 1.36 | 1.95 | 157.68 | 1.43 | 0.38 | 1.75 | 164.70 | -0.33 | 0.13 | 1.17 | 161.06 | 0.39 |
| 10 | 103.86 | -3.77 | 6.70 | 104.12 | -4.13 | 2.67 | 3.15 | 103.34 | -3.19 | 0.40 | 3.51 | 103.21 | 2.45 |
| 1' | 130.83 | -0.11 | 0.77 | 121.61 | -0.85 | -7.08 | 0.91 | 130.97 | 0.45 | -5.85 | 0.39 | 109.45 | 5.01 |
| 2' | 126.48 | -0.26 | -0.26 | 128.63 | 0.19 | -0.19 | -0.84 | 129.08 | -0.13 | -0.07 | -0.06 | 156.96 | 6.63 |
| 3' | 129.27 | 0.33 | -0.07 | 116.28 | 1.30 | 3.05 | -0.39 | 116.47 | 0.00 | 3.19 | -0.01 | 103.67 | 2.86 |
| 4' | 132.13 | -2.53 | -0.07 | 161.19 | 2.73 | 10.92 | -1.30 | 158.52 | -0.19 | 10.01 | -0.07 | 160.60 | -0.20 |
| 5' | 129.27 | 0.33 | -0.07 | 116.28 | 1.30 | 3.05 | -0.39 | 116.47 | 0.00 | 3.19 | -0.01 | 107.05 | -2.67 |
| 6' | 126.48 | -0.26 | -0.07 | 128.63 | 0.19 | -0.19 | -0.84 | 129.08 | -0.13 | -0.07 | -0.06 | 131.68 | -2.27 |

a) Shifts for the phenols (0.8±0.2 M) in ppm vs.TMS, DIS in the phenolates after subsequent additions of 1 Mol NaOH per OH;

b) Measured in $DMSO/D_2O$ (80:20);

c) Measured in $MeOH/D_2O$ (80:20).



C

Our DIS values clearly require a revision of the reported[8] C5 and C9 assignments in chrysin (A) and apigenin (B).

## References and Notes

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2. Cf.a) G.E.Maciel and R.V.James, J.Am.Chem.Soc., 86, 3893 (1964) b) T.T. Nakashima and G.E.Maciel, Appl.Spectr., 26, 220 (1972) c) G.E.Maciel and J.J.Natterstad, J.Chem.Phys., 42, 2427 (1965) d) R.Haran, F.Nepveu-Juras and J.P.Laurent, Org.Mag.Res., 12, 153 (1979) e) M.Ilczyszyn, Z.Latajka and H.Ratajczak, Org.Mag.Res., 16, 173 (1981) f) S.Berger, Tetrahedron, 37, 1607 (1981).
3. Thus, the following shift differences (ppm) were found (relative to 0.045 M phenol in THF): a) 3.2 M in THF: C-1 -2.1, C2,6 0.00, C3,5 +0.33, C4 +1.37; b) 3.68 M in MeOH/$D_2O$ (80:20): -0.05, +1.32, +1.64, +2.23; C) 3.49 M in dioxane/$D_2O$ (80:20) -0.15, +0.83, +1.15, +1.35; d) 2.29 M in dioxane/$D_2O$ (80:20) with KOH instead of NaOH: +10.38, +3.59, -0.22, -6.30.
4. With pyrogallol 14 we observe stepwise DIS after addition of 1 Mol NaOH, although deprotonation of the other OH groups occurs almost simultaneously. 15, however, with 1 Mol NaOH shows 3 broad signals ($W_{1/2} \approx 40$Hz) which sharpen upon addition of a second Mol NaOH and remain unchanged upon further addition of NaOH;(signals at 196.03 ppm from TMS, S in SFORD spectrum; at 185.56, S; at 100.35, D; intensity ratio ~1:1:3). Although some unidentified side product is formed from 15, the reaction is reversible upon addition of HCl. For C-NMR shifts of related cyclohexadienone structures (although not dianions) see: J.M.Brittain, P.B.D.de la Mare and P.A.Newman, J.Chem.Soc. Perkin II, 1981, 32, and references cited therein.
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7. Due to decomposition of the samples at higher pH it is sometimes difficult to observe all deprotonated species ,as in the case of morin or other polyhydroxy compounds.[2d,6]
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