Communications

Carbon-13–Proton Long-Range Couplings of Phenols Hydrogen Bonding and Stereospecificity[1]

Summary: The long-range $^{13}C-^{1}H$ coupling constants of phenol and its ortho-substituted derivatives (salicylaldehyde, salicylic acid, methyl salicylate, and *o*-hydroxyacetophenone) and the stereospecific effect of the intramolecular hydrogen bonding on the long-range couplings are studied.

Sir: The analysis of carbon-13 magnetic resonance (^{13}C NMR) spectra of aromatic molecules has traditionally been accomplished on the basis of the additivity principle. But the effects of individual substituents (shielding constants) are not always additive, particularly for ortho-substituted compounds.[2] This usually leaves some uncertainty in the assignments, which has previously been overcome by other means.[1-4] However, a better approach to solve this problem is the full utilization of $^{13}C-^{1}H$ coupling patterns. This method has so far been used only scarcely in ^{13}C NMR spectral analysis of complicated molecules, primarily because the determination of $^{13}C-^{1}H$ long-range coupling constant was difficult and the number of available long-range coupling constant values of aromatic compounds, especially nonheterocyclic molecules, is limited.[5]

One of the commonly encountered reactions which are fast on the NMR time scale is the intermolecular hydrogen exchange of labile protons between hydroxy groups. Dimethyl sulfoxide has been used as a solvent to inhibit proton exchange of alcohols in ^{1}H NMR.[6] A similar phenomenon can also be observed in ^{13}C NMR.[7] The measurement of the ^{13}C–OH coupling constants depends on the acidity or the exchange rate of the hydroxy proton. No ^{13}C–OH coupling can be detected, even in dimethyl sulfoxide solution, as evidenced by the fact that the identical spectra were obtained for phenol and deuteriophenol (OD) in deuteriochloroform and deuteriodimethyl sulfoxide solutions. The proton coupled spectra of phenol can be fully analyzed if Roberts' conclusion regarding the aromatic $^{13}C-^{1}H$ long-range coupling constants are accepted[5a] (Table I). It is interesting that $^{3}J_{CH}$ through an oxygen-substituted carbon is considerably reduced,[8] which has diagnostic value for analyzing very complicated spectra. Further studies of ortho-substituted phenols can thus be carried out (Table II).

Table I. $^{13}C-^{1}H$ Coupling Constants (hertz) of Phenol in $CDCl_3$[a]

	Carbon			
	1	2	3	4
Multiplicity	ttd	ddd	dd	dt
J (coupled proton)	8.9 (H_3) 2.5 (H_2) 1.3 (H_4)	158.5 (H_2) 7.8 (H_4) 4.2 (H_6)	160.1 (H_3) 8.4 (H_5)	161.6 (H_4) 7.3 (H_2)

[a] Maximum resolution, 0.24 Hz.

Simple chemical shift theory often leaves an ambiguity with respect to the differentiation of the C_4 and C_6 resonance signals of the above compounds.[9] Even the coupling patterns of the C_4 and C_6 signals in the proton-coupled spectrum of salicylaldehyde in deuteriodimethyl sulfoxide solution are identical. However, a clear distinction can be made in the spectrum in deuteriochloroform solution (Figure 1a). The high field portion of C_6 signal gives an extra splitting of which probably results from the coupling with the hydroxy proton, whose exchange rate is greatly reduced by the intramolecular hydrogen bonding.[10] This is confirmed by the disappearance of this extra splitting in the spectrum of deuteriosalicylaldehyde (OD) (Figure 1b). This hydrogen bond is still retained in deuterioacetone solution. This means that ^{13}C NMR can

Table II. ^{13}C Chemical Shifts (δ) and $^{13}C-^{1}H$ Coupling Constants of Phenols[a]

	Carbon						
	1	2	3	4	5	6	7
			Salicylaldehyde (**1**) in $CDCl_3$				
δ (multiplicity)	160.9 (m)	120.3 (m)	133.4 (ddd)	119.5 (dd)	136.5 (dd)	117.0 (dtt)	196.2 (dd)
J (coupled proton)			159.8 (H_5) 8.8 (H_3) 1.0 (H_4)	165.5 (H_4) 7.9 (H_2)	161.0 (H_3) 8.7 (H_5)	162.7 (H_2) 7.5 (H_4) 7.5 (OH) 1.6 (H_3) 1.6 (H_5)	177.2 (H_{CO}) 6.0 (H_5)
			Salicylic Acid (**3**) in Acetone-d_6				
δ (multiplicity)	162.2 (tdd)	112.4 (ddd)	130.5 (dddd)	119.1 (ddd)	135.9 (ddd)	117.3 (ddd)	171.9 (dt)
J (coupled proton)	9.2 (H_3) 9.2 (H_5) 3.3 (H_2) 1.6 (H_4)	8.2 (H_4) 5.1 (H_6) 1.4 (H_5)	162.0 (H_5) 5.6 (H_3) 2.7 (H_4) 0.9 (H_2)	163.6 (H_4) 8.1 (H_2) 1.0 (H_3 or H_5)	160.8 (H_6) 9.3 (H_5) 0.8 (H_2 or H_4)	162.5 (H_6) 7.6 (H_4) 1.2 (H_5)	3.5 (H_5) 1.0 (H_4) 1.0 (H_2)
			Methyl Salicylate (**4**) in $CDCl_3$				
δ (multiplicity)	161.0 (m)	111.6 (dt)	129.1 (ddd)	118.2 (ddd)	134.7 (dd)	116.6 (dt)	169.7 (m)
J (coupled proton)		8.3 (H_4) 4.4 (H_6) 4.4 (OH)	161.9 (H_5) 8.2 (H_3) 3.1 (H_4)	162.8 (H_4) 8.1 (H_2) 1.2 (H_3 or H_5)	160.7 (H_3) 9.3 (H_5)	162.4 (H_2) 7.7 (H_4)	

[a] Small coupling constants (<0.8 Hz) are not included. Maximum resolution, 0.24 Hz; δ (parts per million) downfield from TMS; m, unresolved multiplet.

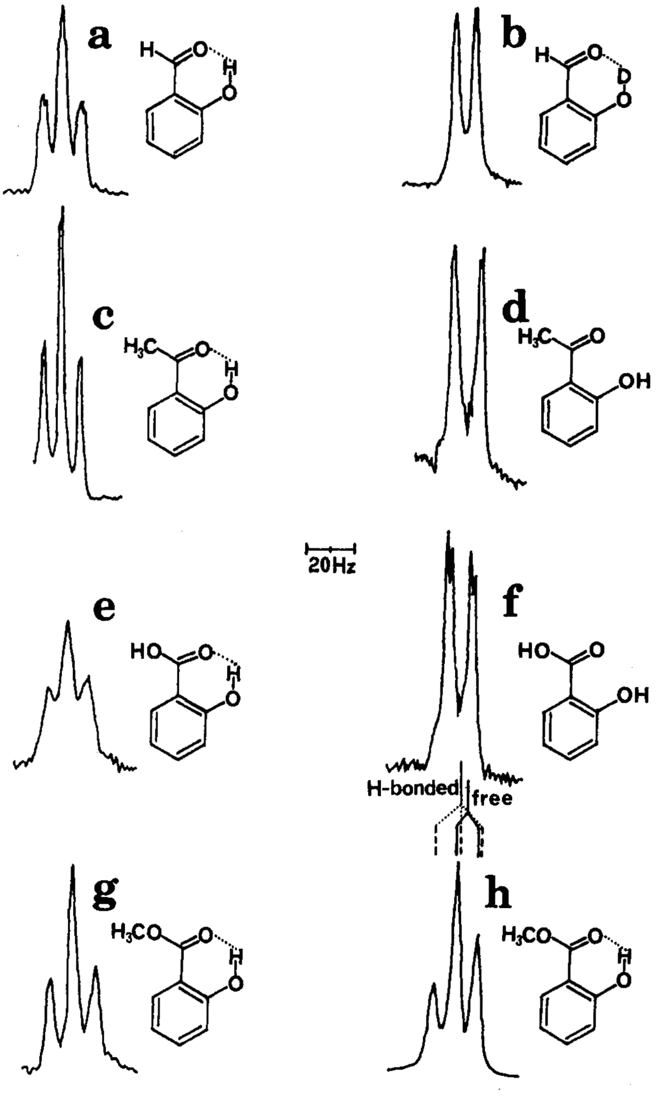
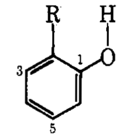


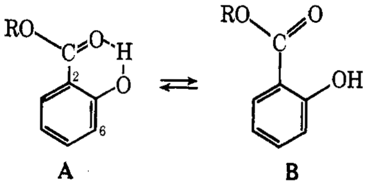
Figure 1. The high field portion of the C_6 signal of ortho-substituted phenols: (a) salicylaldehyde in $CDCl_3$; (b) deuteriosalicylaldehyde (OD) in $CDCl_3$; (c) *o*-hydroxyacetophenone in $CDCl_3$; (d) *o*-hydroxyacetophenone in Me_2SO-d_6; (e) salicylic acid in ethyl ether; (f) salicylic acid in acetone-d_6; (g) methyl salicylate in $CDCl_3$; (h) methyl salicylate in Me_2SO-d_6. The small splittings (<1 Hz) are due to two-bond coupling.

also provide us a direct method to measure the relative strength of intra- vs. intermolecular hydrogen bondings in different solvents. *o*-Hydroxyacetophenone (**2**) gave similar results (Figure 1c and 1d). The C_6 signal of salicylic acid (**3**)



1, R = CHO
2, R = CH_3CO
3, R = CO_2H
4, R = CO_2CH_3

in deuterioacetone solution appears as double doublet (Figure 1f) indicating the absence of intramolecular hydrogen bonding or rapid equilibration between the conformers **3A** and **3B**,



which may be due to the catalytic function of the carboxyl proton in enhancing the equilibration rate.

Many investigators in the field of physical organic chemistry have been concerned about the poor correlations obtained by the Hammet σ–ρ approach[11] for rate or equilibrium data of ortho-substituted benzene derivatives. A mathematical separation of these interactions in a linear fashion is often difficult and unrewarding.

The studies of meta- and para-substituted phenols in dimethyl sulfoxide solution have demonstrated a linear correlation of the hydroxyl chemical shifts with Hammett σ^- constants.[12] Tribble and Traynham[13] thus attempted to give an unambiguous mathematical description of the electronic or proximity effect of ortho substituents by determining ortho-substituent constants (σ_o^-) from the chemical shift measurements of the strongly intermolecularly hydrogen-bonded phenolic proton in dimethyl sulfoxide solution. Two extreme deviations (o-NO_2, and o-$COCH_3$) were ascribed to intramolecular hydrogen bonding, but, from the proton coupled spectrum of acetophenone (**2**) in the "regular" deuteriodi-

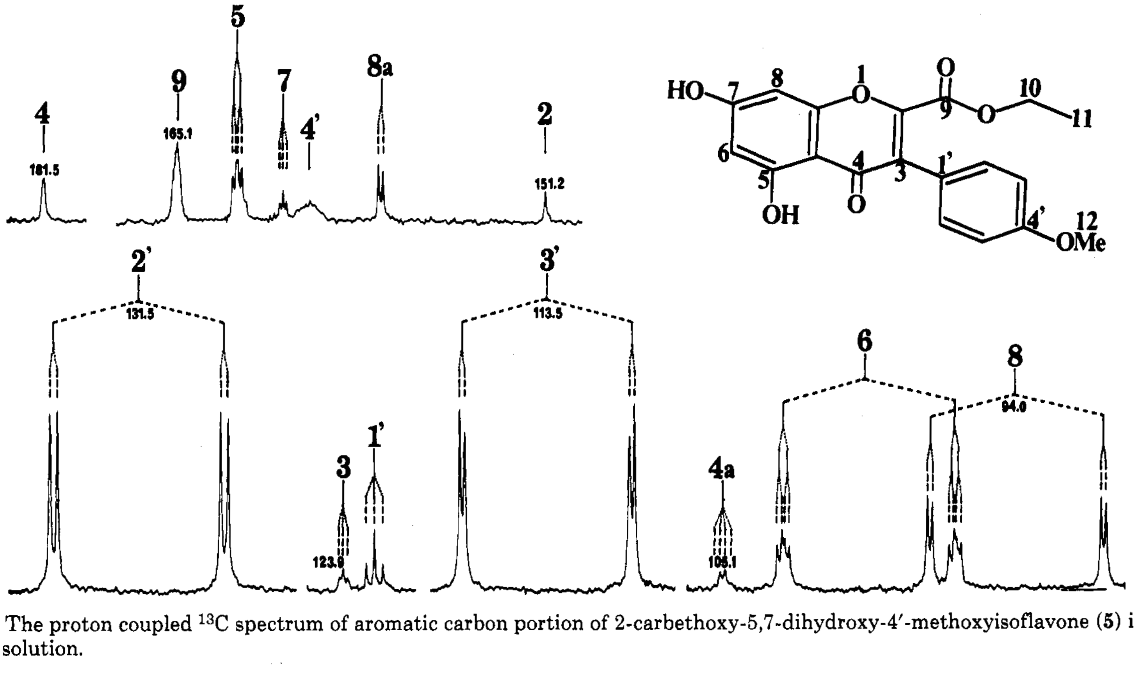
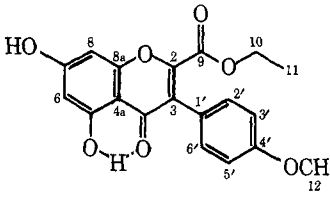


Figure 2. The proton coupled ^{13}C spectrum of aromatic carbon portion of 2-carbethoxy-5,7-dihydroxy-4′-methoxyisoflavone (**5**) in deuterioacetone solution.

methyl sulfoxide solution [50% (v/v)] (Figure 1d), the presence of a significant amount of the conformer (**2B**) is clearly indicated. They also stated that methyl salicylate (**4**) did not form an intramolecular hydrogen bond to any significant degree. In contrast, the ^{13}C NMR spectra of methyl salicylate in the same "regular" deuteriodimethyl sulfoxide solution [50% (v/v)] clearly reveals the existence of the intramolecularly hydrogen-bonded conformer (**4A**) (Figure 1g and 1h), which is in accord with Curtin's and Byrn's infrared study.[14] The ratio of these two representative conformers (**4A**/**4B**) is 1.77.[15] Their equilibration rate is enhanced by acid and depends on temperature. At 118 °C the C_1 signals of **4A** (160.9 ppm at 25°C) and **4B** (160.7 ppm at 25 °C) coalesce, and the ^{13}C–^{1}H three-bond coupling vanishes. In view of these discrepancies, it must be cautioned against the use of the ortho-substituent constants derived from the earlier ^{1}H NMR studies.[12] Among the results of the complete analysis of the ^{13}C–^{1}H long-range coupling constant it is worth noting that the syn ^{13}C–^{1}H coupling constant ($^3J_{C_2-OH} = 4.4$ Hz) is considerably smaller than the anti coupling constant ($^3J_{C_6-OH}$ 8.3 Hz), analogous to the olefinic system.[5e] Therefore, ^{13}C–^{1}H long-range coupling constants can be useful in the conformational study of the hydroxy functional group.

The complete analysis of the ^{13}C spectrum of an isoflavone derivative (**5**) can further illustrate the potential usefullness of ^{13}C–^{1}H long-range coupling constants (Figure 2).[16] Using the additivity principle of chemical shift theory, it is difficult to differentiate C_5, C_7, C_{8a}, and $C_{4'}$ and to distinguish the C_8 from C_6, and C_3 from $C_{1'}$ resonance signals. However, the detailed analysis of the long-range ^{13}C–^{1}H coupling constants allows one to completely resolve these ambiguities. In the proton-coupled spectrum in deuterioacetone solution, $C_{4'}$ shows as an unresolved multiplet at 160.2 ppm due to coupling with the methoxy protons, $H_{2'}$ and $H_{6'}$, and possibly with $H_{3'}$ and $H_{5'}$. C_{8a} has only one two-bond proton (H_8) and thus appears as a doublet at 157.5 ppm. A triplet at 161.1 ppm can be assigned to C_7, since only this carbon possesses two two-bond protons (H_6 and H_8). The C_5 signal is split into a double doublet owing to the coupling with H_6 and hydroxy proton which strongly indicates the intramolecular hydrogen bonding between this hydroxy group and the C_4 carbonyl group. This hydrogen bonding also results in the further splitting of C_6 signal ($^3J_{C_6-OH} = 7.0$ Hz), which is shown as double doublet of doublets at 99.6 ppm while the C_8 signal appears as double doublet at 94.0 ppm. C_{4a} is shown as a quartet due to the long-range coupling with H_6, H_8, and C_5–OH protons. Here, the stereospecificity of the three-bond ^{13}C–^{1}H coupling is disclosed again [$^3J_{C_{4a}-OH} = 4.3$ Hz (syn); $^3J_{C_6-OH} = 7.0$ Hz (anti)]. $C_{1'}$ can be easily distinguished from C_3 by its normal three-bond coupling constant ($^3J_{C_{1'}-H_{3'(5')}} = 8.0$ Hz), whereas the $^3J_{C_3-H_{2'(6')}}$ is reduced to 4.0 Hz. The carbons $C_{3'(5')}$ couples with $H_{5'(3')}$ through the oxygen-substituted carbon. The singlet at 151.2 ppm is assigned to C_2 simply because it is the only aromatic carbon without any two- or three-bond proton.



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Reference and Notes

(1) Part of this communication was presented at the 16th Annual Meeting of the Phytochemical Society of North America, "Spectral analysis of flavonoids", Aug 4–7, 1975, Tampa, Fla.

(2) (a) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1971; (b) G. C. Levy and G. L. Nelson, "Carbon-13 Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y. 1972.

(3) E. Wenkert, J. S. Bindra, C.-j. Chang, D. W. Cochran, and F. M. Schell, *Acc. Chem. Res.*, **7,** 46 (1974).

(4) (a) N. J. Bach, H. E. Boaz, E. C. Kornfeld, C.-j. Chang, H. G. Floss, E. W. Hagaman, and E. Wenkert, *J. Org. Chem.*, **39,** 1272 (1974); (b) N. Neuss, C. H, Nash, P. A. Lemke, and J. B. Grutzner, *J. Am. Chem. Soc.*, **93,** 2337 (1971).

(5) (a) F. J. Weigert and J. D. Roberts, *J. Am. Chem. Soc.*, **89,** 2967 (1967); (b) G. J. Karabatsos, J. D. Graham, and F. Vane, *J. Am. Chem. Soc.*, **84,** 37 (1962); (c) G. Govil, *J. Chem. Soc. A*, 1420 (1967); (d) A. R. Tarpley and J. H. Goldstein, *J. Mol. Spectrosc.*, **39,** 275 (1971); (e) J. L. Marshall, D. E. Miiller, S. A. Conn, R. Seiwell, and A. M. Ihrig, *Acc. Chem. Res.*, **7,** 333 (1974), and other references therein.

(6) O. L. Chapman and R. W. King, *J. Am. Chem. Soc.*, **86,** 1256 (1964).

(7) ^{13}C–$O^{1}H$ coupling constants of ethanol in deuteriodimethyl sulfoxide solution were measured. It is of interest to note that the $^3J_{C-C-O-H}$ (3.1 Hz) is larger than $^2J_{C-O-H}$ which is analogous to ^{13}C–^{1}H coupling constants of normal aromatic system.[5a] It may be profitable to further investigate this long-range coupling to gain information about the steric environments of hydroxy function [(a) E. F. Keifer, W. Gericke, and S. T, Amimoto, *J. Am. Chem. Soc.*, **90,** 6246 (1968); (b) N. L. Bauld and Y. M. Rim, *J. Org. Chem.*, **33,** 1303 (1968); (c) R. D. Storvlow and A. A. Gallo, *Tetrahedron Lett.*, 3331 (1968), and other references therein], particularly the keto–enol tautomerism and the conformational analysis of cyclic alcohols in conjunction with lanthanide shift reagents which are currently pursued this laboratory.

(8) (a) From a large number of accumulation of high resolution spectra of aromatic compounds, this conclusion may be held for most electronegative substituents. Further results will be published soon. (b) First-order analysis was carried out. However the spectra of *o*-hydroxyacetophenone (**2**) appear non first order, and further detailed calculation will be necessary to unravel its precise long-range coupling constants.

(9) L. F. Johnson and W. C. Jankowski, "Carbon-13 NMR Spectra", Wiley-Interscience, New York, N.Y., 1972.

(10) In ether solution, this interconversion is considerably reduced; thus the intramolecular hydrogen bonding can be detected under this condition (Figure 1f), but the $^3J_{C-OH}$ (6.6 Hz) is smaller than the normal value (~7.4 Hz) suggestive of the moderate exchange rate between the two conformers.

(11) L. P. Hammett, "Physical Organic Chemistry", McGraw-Hill, New York, N.Y., 1940, Chapter VII.

(12) (a) J. G. Traynham and G. A. Knesel, *J. Org. Chem.*, **31,** 3350 (1966); (b) R. J. Ouellette, *Can. J. Chem.*, **43,** 707 (1965).

(13) M. T. Tribble and J. G. Traynham, *J. Am. Chem. Soc.*, **91,** 379 (1969).

(14) D. Y. Curtin and S. R. Byrn, *J. Am. Chem. Soc.*, **91,** 6102 (1969).

(15) The ratio seems to depend on the concentration. However, the critical factor is the water content in the laboratory deuteriodimethyl sulfoxide. The "regular" deuteriodimethyl sulfoxide used in the experiments contains 0.2–0.3% (w/w) water. Only intramolecular hydrogen-bonded conformer can be detected in "dry" deuteriodimethyl sulfoxide (distilled over calcium hydride twice just prior to use) solution. All ^{13}C NMR spectra were obtained in 10-mm spinning tube at ambient temperature (~25 °C). The ^{13}C resonances of deuteriodimethyl sulfoxide, deuterioacetone, and deuteriochloroform serve as internal references.

(16) Very recently Wehrli and Kinsbury also applied the long-range couplings in their partial spectral analysis of flavonoids: (a) F. W. Wehrli, *J. Chem. Soc., Chem. Commun.*, 663 (1974); (b) C. A. Kingsubury and J. H. Looker, *J. Org. Chem.*, **40,** 1120 (1975).

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Received January 12, 1976

Carbon Acids. 8. The Trimethylammonio Group as a Model for Assessing the Polar Effects of Electron-Withdrawing Groups

Summary: The relative size of polar and resonance contributions for CH_3CO, PhCO, $PhSO_2$, CN, and NO_2 groups in stabilizing a number of carbanions has been assessed from equilibrium acidity measurements by using the trimethylammonio group, Me_3N^+, as a model for the polar effect.

Sir: The trimethylammonio group, Me_3N^+, is unique in that it exerts a strong polar action and yet is incapable of acting as a π acceptor. As such, it has frequently been used as a model for judging the polar character of electron-withdrawing groups, G, and, from this, the extent to which G is capable of acting as a π acceptor when interacting with an acidic site across a benzene ring, as in p-$GC_6H_4NH_3^+$ or p-GC_6H_4OH.[1-3] We now wish to report results in which the effect of Me_3N^+ is used as a model to assess the resonance vs. polar character