Two-Bond Deuterium Isotope Effects on ^{13}C Chemical Shifts of Phenols

Yasuki NAKASHIMA, Akihiro YOSHINO, and Kensuke TAKAHASHI*
Department of Applied Chemistry, Nagoya Institute of Technology, Gokiso-cho, Showa-ku, Nagoya 466
(Received September 14, 1988)

Two-bond deuterium isotope effects on ^{13}C chemical shifts of 28 substituted phenols are reported and explained in terms of the additivity of substituent parameters which are correlated with the SCS of ^{13}C NMR.

Deuterium isotope effects on ^{13}C chemical shifts are useful parameters for spectral assignments, kinetic studies, and biomechanic studies.[1] The cause of the effect is still unclear, especially regarding further remote effects over one-bond.[2–5] If the magnitudes of the shifts are correlated with any molecular parameters, their applications would be extended in further use. Among such isotope effects, the long-range effects, however, have rarely been reported for aromatic compounds.[6,7] Therefore, more data must be accumulated.

In this study, 28 substituted phenols were selected for the purpose of studying two-bond isotope effects on ^{13}C NMR shifts. One of the reasons for our selection was for an easy preparation of deuterium-labeled compounds. From the sixty nine data points obtained, substituent isotope shifts (hereafter abbreviated as SIS) for seven substituents were quantitatively determined. The SIS's are correlated linearly with the SCS's of the aromatic carbons. Then, the two-bond isotope shifts ($^2\Delta$) can be evaluated from the knowledge of the SCS's. They can also be correlated with the electron densities of the sites under study.

Experimental

Deuterium-labeled compounds were prepared with acid- or base-catalyzed proton–deuteron exchange-reactions of substituted phenols.[8] The starting materials used were commercially available and were used without further purification. Reaction vessels were hand-made Pyrex ampoules. About 0.01 mol of a starting material and a small amount of catalyst (0.1 wt%) dissolved in 1 g of D_2O were sealed into the ampoule, and kept at 80 °C in the thermostatted air oven. After the reaction had reached an extent of about 5—50 D%, the sample was cooled by immersing it in water; the contents were then separated into aqueous and oily (or solid) phases. The latter phase was used for an NMR measurement. Protium–deuterium exchange reactions occurred at 2, 4, and 6-positions and not at 1, 3, and 5-positions of the substituted phenols when they were examined with NMR spectroscopy. The hydroxyl hydrogen of phenol exchanges with that of water and cannot be separately observed on the NMR time scale. Then, the labeled substituent such as OD, ND_2, or NHD did not have any effect on the ^{13}C chemical shifts, as described by Newmark and Hill.[9] Other substituents did not suffer any exchange. Therefore, one- and three-bond isotope effects were observed at the C_2, C_4, and C_6 atoms on the ^{13}C spectra. However, the carbon signals were broadened by the quadrupole effect of deuteron. Thus, accurate values of their isotope effects could not be determined. However, two- and four-bond isotope effects were observed at the C_1, C_3, and C_5 signals. In their spectra two-bond carbon–deuteron couplings are negligibly small and seem to have no effect on their line-widths. An example of the measurement is given in Fig. 1. For the purpose of observing the isotope effect, the extent of the reaction was devised to be nearly 50%. If this is so, the labeled and unlabeled phenols are suitably mixed for their NMR measurements, as shown in Fig. 1. Therefore, the $^2\Delta$ values can be evaluated by using the data obtained from the labeled and unlabeled phenols in a solution contained in the same NMR tube. This might be helpful for decreasing the experimental error of the measurement, which was evaluated to be within 5 ppb. Six C_1 or C_3 signals were observed in Fig. 1. The assignments of the six signals were carried out according to changes in their heights with time. At the starting time of the proton–deuteron exchange reaction only the most downfield signal was observed. When the reaction proceeded with time, five upfield signals appeared in the spectra with gradually increasing heights. Then, the substituent effect of deuteron is an upfield shift. It was also assumed that in polydeuterated compounds deuterons exert their effects additively. If this is so, the six

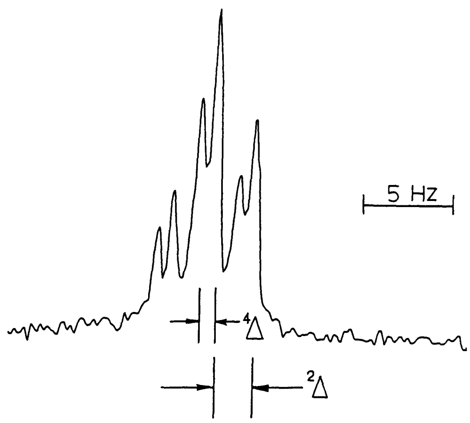

Fig. 1. ^{13}C NMR signals of C_1 or C_3 atoms of the products obtained from the proton–deuteron exchange reaction of 1,3-benzenediol in a 0.14 wt% NaOH–D_2O solution. The signals were averaged for 64 scans. The six signals are assigned as coming from (a) 2,4,6-trideuterated, (b) 2,4- or 2,6-dideuterated, (c) 2,4-, 4,6-, or 2,6-dideuterated, (d) 2- or 6-deuterated, (e) 4-deuterated, and (f) undeuterated 1,3-benzenediols from the right-hand to the left-hand side.

signals can be assigned straightforwardly. The six signals are divided into three groups with a splitting of $^2\Delta$. The three groups can be assigned as those in which the two adjacent sites of the C_1 of the sample have two H's, one H and one D, and two D's. Each of the three groups shows a further small splitting of $^4\Delta$. The six signals were then assigned to be signals coming from (a) 2,4,6-trideuterated, (b) 2,4- or 2,6-dideuterated, (c) 2,4-, 4,6-, or 2,6-dideuterated, (d) 2- or 4-deuterated, (e) 4-deuterated, and (f) undeuterated 1,3-benzenediols from the right-hand (upfield) to the left-hand side (downfield). The value of $^2\Delta$ can be evaluated from the difference of two signals, for example a and c, or c and e. Four-bond isotope effects were accidentally observed in the sample shown in Fig. 1. However, they were generally not determined because of their small magnitudes.

NMR spectra were measured with a Varian XL-200 FT-NMR spectrometer at 50.3 MHz and at about 22 °C. The concentration of the NMR sample solution was neat for the liquid sample and ca. 50 wt%, mostly in dioxane or any other solvent for the solid sample. The ^{13}C NMR spectra were measured by using a gated decoupling technique with no NOE pulse sequence. Data acquisition was carried out under the following conditions: a 45° flip angle of pulse, 24—128 transients, 32000 data points, a delay time of 40 s, and a spectral width of 2600—3500 Hz. Linear regression calculations of the experimental data were carried out on an NEC PC9801VX personal computer in our laboratory using a BASIC program. Details of acid- or base-catalyzed proton–deuteron exchange reactions will be published elsewhere.

Results and Discussion

Sixty-nine two-bond isotope effects of 28 phenols were determined. They are in a range from 32 to 112 ppb (Table 1). All of the observed two-bond isotope effects were toward the high filed. Therefore, the values given in Table 1 should be negative in the conventional manner. However, the signs are neglected in the table. As can be seen in Table 1, the values of $^2\Delta$ of the C_1's are always smaller than those of the C_5's. The values of the C_3's are intermediate between those of the C_1's and C_5's, except for several cases. The $^2\Delta$'s are then correlated with the ^{13}C chemical shifts, which are cited from several articles,[10—13] as shown in Fig. 2. $^2\Delta$ in ppb can be expressed as follows:

$$^2\Delta(\text{ppb}) = -2.06\,\delta_c(\text{ppm}) + 365. \tag{1}$$

The $^2\Delta$ are roughly related to the ^{13}C chemical shifts. Therefore, their correlation with kinds of substituents might be considered. Then, the contributions of the various substituents to the two-bond isotope shifts were determined by linear regression analyses using

$$^2\Delta = B_0 + n_i a + n_o b + n_m c, \tag{2}$$

where B_0 is the two-bond isotope shift of the unsubstituted benzene (cited as 111 ppb[7]). Three parameters (a, b, and c) are the contributions from ipso, ortho, and meta positioned substituents, respectively. n_i, n_o, or n_m is a weight factor for each substituent parameter. An example of a calculation

Table 1. Two-Bond Deuterium Isotope Effects on ^{13}C Chemical Shifts of Substituted Phenols in ppb[a)]

No.	Substituent	Solvent	C-1	C-3	C-5
1	None	Neat	44	107	107
2	2-Me	Neat	39	105	112
3	3-Me	Neat	47	84	107
4	4-Me	Neat	43	96	96
5	2,3-Me_2	1,4-Dioxane	42	84	111
6	2,4-Me_2	Neat	43	—	105
7	2,5-Me_2	1,4-Dioxane	38	111	86
8	2,6-Me_2	1,4-Dioxane	—	111	111
9	3,4-Me_2	1,4-Dioxane	46	76	101
10	3,5-Me_2	1,4-Dioxane	45	86	86
11	2-OMe	Neat	39	105	109
12	3-OMe	Neat	48	46	107
13	4-OMe	Neat	51	92	92
14	2,3-$(OMe)_2$	Neat	47	42	110
15	2-Cl	Neat	38	99	108
16	3-Cl	Neat	46	88	106
17	4-Cl	Neat	45	91	91
18	2,3-Cl_2	1,4-Dioxane	40	83	106
19	3,4-Cl_2	1,4-Dioxane	48	76	b)
20	3,5-Cl_2	Neat	50	86	86
21	2-*t*-Bu	$CDCl_3$	32	108	108
22	3-*t*-Bu	Neat	40	66	100
23	4-*t*-Bu	Neat	44	101	101
24	3-OH	0.14 wt% NaOH–D_2O	47	47	107
25	2-NO_2	D_2O	b)	110	102
26	3-NO_2	CH_3OH	54	61	97
27	4-NO_2	CH_3OH	b)	98	98
28	3-NH_2	0.10wt% HCl–D_2O	43	63	104

a) Errors are estimated to be within 5 ppb. b) Not available.

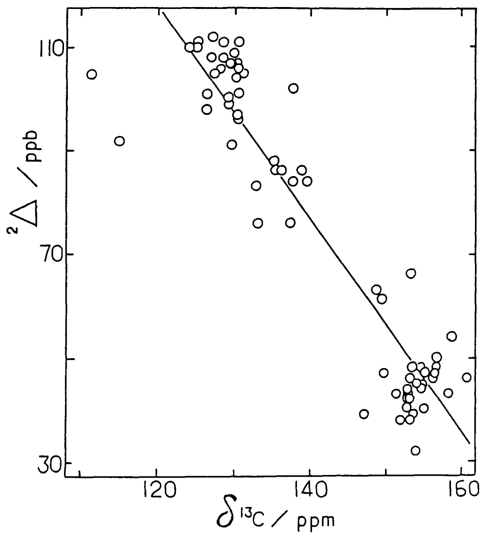

Fig. 2. Correlation between $^2\Delta$ (ordinate in ppb) and δ_c (abscissa in ppm) for substituted phenols with r=0.932 and the standard deviation of 10.4 ppb.

Table 2. Statistical Parameters for Eq. 2[a)]

Parameter	Substituent						
	OH	OMe	*t*-Bu	Me	Cl	NO_2	NH_2
a	−64.8	−60.3	−41.5	−22.7 (−26.4)[b)]	−19.7	−46.5	−44.5
b	−3.0[c)]	−6.5	−6.8	−4.1 (−5.5)	−9.5	−3.5	d)
c	−3.5	2.8	−6.9	0.3 (0)	0.8	−1.4	−3.4

a) RMS error=4.4 ppb. Linear correlation coefficient between experimental and calculated data=0.991. Standard deviation=3.8 ppb. b) The value in parentheses is cited from Ref. 7. c) See text. d) Not available.

using Eq. 2 with three substituent parameters and three weight factors can be illustrated as follows. An example is 1,3-benzenediol (**24**). Its C_1 is affected by a directly bonded substituent and a meta-positioned one. Its C_5 is affected by two meta-positioned substituents. Therefore, its calculated $^2\Delta$ can be expressed as follows:

1,3-position: $n_i = 1$, $n_o = 0$, and $n_m = 1$;

$$^2\Delta = B_0 + a + c;$$

5-position : $n_i = 0$, $n_o = 0$, $n_m = 2$;

$$^2\Delta = B_0 + 2c.$$

The experimentally observed values given in Table 1 are used to evaluate these parameters for each substituent by using linear regression analyses. The parameters obtained for seven kinds of substituents are given in Table 2. These parameters (*a*, *b*, and *c*) are called Substituent Isotope Shift (SIS). The observed two-bond isotope shifts can be calculated with Eq. 2 by using these SIS values with an RMS error of 4.4 ppb and a correlation coefficient of 0.991. So far, a similar analysis has been reported only for one substituent of the CH_3 group by Berger et al.[7)] They explained that two-bond isotope shifts for CH_3 can be obtained by two parameters, *a* and *b*, which are consistent with our values given in Table 2. Although the value is rather small, one additional parameter of *c* is included in our analysis.

Correlation between SIS and SCS for ^{13}C NMR. The parameters of SIS decrease in magnitude from *a*, *b*, to *c*. All values of *a* and *b* are large and negative. However, *c* is rather small and either positive or negative. This means that $^2\Delta$ becomes small when any substituent is introduced in the aromatic ring. The magnitudes of *a* are in an order OH>OMe>NO_2>NH_2>*t*-Bu>Me>Cl. This order is parallel to that of the SCS values of the ^{13}C NMR. The SIS values of seven substituents are plotted in Fig. 3, correlated with the SCS values of ^{13}C NMR.[14)] As can be seen in Fig. 3, the points are linearly correlated, except for those of the ortho-positions, which are shown by black-filled circles. The correlation coefficient gives a rise from 0.924 to 0.980 when the points of the ortho-positions are excluded. Therefore, both the SIS's and the SCS's are linearly correlated with each other at the ipso and meta positions. This fact means that the factors controlling the SIS's are partly the same as those of the SCS's. Especially the deviation of the black-filled circles are downward from the correlated straight line. The magnitudes of their deviations are in the order OMe>NO_2>*t*-Bu>Cl>Me. Therefore, the deviation seems to be affected by a steric effect of bulky substituents, such as OMe, NO_2, and *t*-Bu groups. The ^{13}C chemical shifts sometime suffer a steric compression effect from bulky substituents.[15,16)] The isotope effect, on the contrary, is said not to suffer such a contribution.[7)] The deviations of the black-filled circles are thus explained by such steric effects which are effective for SCS but ineffective for SIS. This idea is supported by the fact that the observed deviation of the OMe, NO_2, or *t*-Bu group is given at the negative side of the SCS from a straight line, as can be seen in Fig. 3. Among those black-filled points, however, the

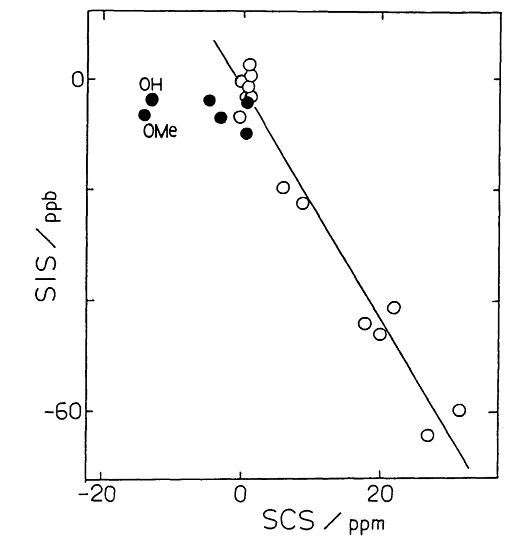

Fig. 3. Correlation between the SIS and SCS values of the ^{13}C NMR determined for substituted phenols. A correlated straight line is expreseed as SIS(ppb)= −2.11 SCS(ppm)−1.30 with r=0.980 and the standard deviation of 5.0 ppb when the black-filled points are excluded.

deviation of OMe is much larger than others. Therefore, it must be necessary to consider other effects. In order to clarify this point we made an examination in order to obtain the value of b for OH. The $^2\Delta$ of m-deuterophenol is 108 ppb.[17] From this value b equals to -3.0 ppb (plotted in Fig. 3). The deviation of OH is similar to that of OMe. Therefore, the origin of the deviation must be explained by other effects, such as the lone pair of the oxygen atom.

Presently, the origins of the isotope shifts are considered to be entirely or partly due to the vibration.[18] However, for deuteromethyl-substituted aromatic compounds two explanations have been presented, in which the hyperconjugational part is reversed in sign to the vibrational one.[2,3,7,19] But in cases where the deuterium atom is directly bonded to the aromatic ring, the hyperconjugational effect is not considered.[20] Furthermore, as shown in Figs. 2 and 3, and Eq. 1, the isotope shifts studied here have been correlated to the chemical shifts of the corresponding carbons. A similar discussion was also presented by Arrowsmith and Kresge.[21] These examples suggest the electron densities of the carbon atoms under study can become the origin of the isotope shifts.

Conclusion

Two-bond isotope shifts for the substituted phenols are represented additively by three parameters assigned to each substituent. This additivity can also be applied to polysubstituted benzenes. Further, the SIS values were correlated with the SCS values of the substituents of ^{13}C NMR. This would be a key for considering the origins of the isotope effect.

References

1) a) P. E. Hansen, *Ann. Repts. NMR Spectr.*, **15**, 105 (1983); b) D. A. Forsyth, "Isotopes in Organic Chemistry," ed. by E. Buncel and C. C. Lee, Elsevier, New York (1984), Vol. **6**, Chap. 1.

2) L. Ernst, H. Hopf, and D. Wullbrandt, *J. Am. Chem. Soc.*, **105**, 4469 (1983).

3) J. R. Wesener and H. Günther, *Tetrahedron Lett.*, **23**, 2845 (1982).

4) R. Aydin and H. Günther, *J. Am. Chem. Soc.*, **103**, 1301 (1981).

5) K. L. Servis and R. L. Domenick, *J. Am. Chem. Soc.*, **108**, 2211 (1986).

6) R. A. Bell, C. L. Chan, and B. G. Sayer, *J. Chem. Soc., Chem. Commun.*, **1972**, 67.

7) S. Berger and W. K. Diehl, *Magn. Reson. Chem.*, **24**, 1073 (1986).

8) A. Murry, III and D. L. Williams, "Organic Syntheses with Isotopes," Interscience Publishers, Inc., New York (1958), Part 1, p. 1652.

9) R. A. Newmark and J. R. Hill, *Org. Magn. Reson.*, **13**, 40 (1980).

10) D. A. Netzel, *Org. Magn. Reson.*, **11**, 58 (1978).

11) M. Ilczyzyn, Z. Lstsjka, and H. Ratajczak, *Org. Magn. Reson.*, **13**, 132 (1980).

12) W. B. Smith and T. W. Proulx, *Org. Magn. Reson.*, **8**, 205 (1976).

13) L. F. Johnson and W. C. Jankowski, "Carbon-13 NMR Spectra," John Wiley & Sons, New York (1972), p. 385.

14) D. A. Ewing, *Org. Magn. Reson.*, **12**, 499 (1979).

15) D. M. Grant and B. V. Cheney, *J. Am. Chem. Soc.*, **89**, 5315 (1967).

16) J. B. Grutzner, M. Jautelat, J. B. Dence, R. A. Smith, and J. D. Roberts, *J. Am. Chem. Soc.*, **92**, 7107 (1970).

17) m-Deuterophenol was prepared from m-chlorophenol by using a method described by M. Tashiro et al. (*J. Org. Chem.*, **43**, 196 (1978)).

18) A. Bernheim, *Progr. Nucl. Magn. Reson. Spectr.*, **3**, 63 (1967).

19) S. Berger, B. W. K. Diehl, and H. Künzer, *Chem. Ber.*, **120**, 1059 (1987).

20) S. Berger and H. Künzer, *Tetrahedron*, **39**, 1327 (1983).

21) C. H. Arrowsmith and A. J. Kresge, *J. Am. Chem. Soc.*, **108**, 7918 (1986).