MAGNETIC RESONANCE IN CHEMISTRY, VOL. 24, 1073–1076 (1986)

An Increment System for Deuterium Isotope Effects on ^{13}C Chemical Shifts of Methylated Benzenes

Stefan Berger* and Bernd W. K. Diehl
Fachbereich Chemie der Universität Marburg, Hans Meerwein Strasse, D-3550 Marburg, FRG.

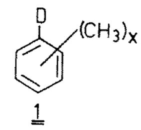
The complete series of all possible benzenes bearing one deuterium atom and one to five methyl groups was synthesized. The deuterium isotope effects on the carbon chemical shifts of the aromatic and aliphatic carbon atoms were measured and shown to obey an empirical increment system. The isotope effects over one bond correlate with the C,H spin coupling constants.

KEY WORDS ^{13}C NMR, deuterium isotope effects, methylbenzenes.

INTRODUCTION

Deuterium isotope effects on ^{13}C chemical shifts have recently gained strong interest,[1] and various mechanisms have been discussed in order to understand their origin.[2] We have shown that long-range deuterium isotope effects can be used to calculate substituent constants for the deuterium atom.[3] If the effects of a deuterium atom can be treated like that of an ordinary polar substituent,[4] one should be able to predict the isotope effects on ^{13}C chemical shifts from an empirical increment system, whose values display steric and electronic factors. Such increment systems exist for a huge number of compounds in the case of ordinary substituents,[5] and it was of interest to us to investigate whether in a closely defined class of compounds such an increment system would also work for deuterium isotope effects.

We chose the group of the 20 possible methylated benzenes **1** substituted with one deuterium atom. This group of compounds forms a set with a well defined geometry on a rigid backbone where conformational problems do not pose a major restriction for the interpretation of isotope effects.[6] Further, for the polymethylated benzenes themselves, an increment system for the ^{13}C chemical shifts has already been published.[7]



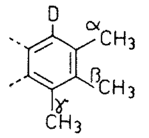
1

RESULTS AND DISCUSSION

The deuterium isotope effects measured for compounds **1** are given in Table 1. The discussion of the deuterium isotope effects will be separated for the aromatic backbone values and the methyl group carbon atoms.

The comparison of deuteriobenzene (**1a**) with the three isotopomeric deuteriotoluenes **1b**, **1c** and **1d** reveals interesting methyl group increments on the $^{1}\Delta$ deuterium isotope effect. An *ortho*-methyl group increases this value by 31 ppb, whereas *meta*- and *para*-methyl groups decrease the $^{1}\Delta$ effect by 3 and 7 ppb, respectively. From these increments the experimental values in the xylenes **1f**, **1g**, **1h** and **1i** can be calculated almost exactly. However, further inspection of Table 1 reveals that additional steric parameters are required to describe the values for the xylene **1e** and the higher substituted compounds when two or more methyl groups are adjacent to each other. We therefore used a linear regression programme to fit the experimental parameters to the equation

$$^{x}\Delta = B_0 + an_\alpha + bn_\beta + cn_\gamma + dn_{\alpha\beta} + en_{\alpha\beta\gamma} \qquad (1)$$



where x is the number of intervening bonds between the deuterium atom and the carbon atom for which the isotope effect is measured. B_0 is the usual basis value and α, β and γ represent the occurrence of a methyl group in an α-, β-, or γ-position relative to the deuterium multiplied by their integer number n. The parameter $\alpha\beta$ represents the steric correction in the case of two adjacent methyl groups in α- and β-positions as, for example, in **1e**. The term $\alpha\beta\gamma$ is the steric correction if three methyl groups are adjacent to each other as, for example, in **1k**.

This increment calculation reproduces the $^{1}\Delta$ isotope effects of the 20 compounds with a standard deviation of 2.9 ppb; the linear correlation coefficient

---

* Author to whom correspondence should be addressed.

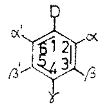
0749–1581/86/121073–04$05.00

Received 23 June 1986
Accepted 24 June 1986

Table 1. Deuterium isotope effects on ^{13}C chemical shifts of monodeuteriated benzenes[a]

1-Deuterio benzene	No.	Ring carbon atoms 1	2	6	3	5	4	Methyl carbon atoms α	α'	β	β'	γ
1-Deuterio	**1a**	283	111	111	11	11						
2-Methyl	**1b**	312	86	110		7		61				
3-Methyl	**1c**	280	106	110	11	7	4					
4-Methyl	**1d**	276	110	110	11	11	7					−3
2,3-Dimethyl	**1e**	309	79	112	9	11	6	66		14		
2,4-Dimethyl	**1f**	299	85	109	2	10	9	62				
2,5-Dimethyl	**1g**	304	85	106	2	11	2	63				
2,6-Dimethyl	**1h**	327	83	83	1	1	8	63	63			
3,4-Dimethyl	**1i**	274	104	111	13	8	10					
3,5-Dimethyl	**1j**	279	105	105	10	10						
2,3,4-Trimethyl	**1k**	306	78	112	10	13	10	69		13		
2,3,5-Trimethyl	**1l**	316	80	108	4	7	6	64		14		
2,3,6-Trimethyl	**1m**	340	79	87	4		7	65	62	13		
2,4,5-Trimethyl	**1n**	298	87	104		12	10	61				
2,4,6-Trimethyl	**1o**	323	83	83			12	63	63			
3,4,5-Trimethyl	**1p**	276	106	106	10	10	11					
2,3,4,5-Tetramethyl	**1q**	306	79	109		13	11	70		13		
2,3,4,6-Tetramethyl	**1r**	327	77	85	9	2	13	70	62	13		
2,3,5,6-Tetramethyl	**1s**	340	79	79	9	9	13	65	65	12	12	
2,3,4,5,6-Pentamethyl	**1t**	340	79	79	10	10	14	70	70	14	14	

[a] Values in ppb, measured in solutions of unequal amounts of deuteriated and undeuteriated compounds. α- and β- and γ-values for methyl carbon atoms clockwise, α'- and β'-values for methyl carbon atoms anticlockwise from the deuterium atom as indicated in the formula



r between the experimental and calculated data is 0.994.

The values of B_0, *a*, *b*, *c*, *d* and *e* are given in Table 2.

The principal similarity between the methyl group increments on carbon chemical shifts as found by Woolfenden[8] and the methyl group increments on isotope effects is significant. For instance, both systems predict for a methyl group in an *ortho* position a positive, in a *para* position a negative and in a *meta* position a negligible contribution. However, Eqn (1) not only reproduces the ${}^1\Delta$ isotope effects, but also describes all other long-range isotope effects in compounds **1**. It is of interest to compare the statistical results within the rows and columns of Table 2.

Table 2. Statistical parameters for Eqn (1)

Parameter	Aromatic carbon atoms				Methyl groups	
x	1	2	3	4	3	4
k^a	20	32	31	20	16	16
B_0	282.8	111.1	9.8	0.1	62.3	0
a	23.7	−26.4	−8.9	2.9	0[d])	0
b	−0.9	−5.5	1.7	1.6	0	0
c	−7.4	0	0	6.1	0	0
d	6.9	0	6.1	0	3.0	13.3
e	1.6	0	0	0	4.5	0
σ^b	2.9	1.4	1.7	2.0	0.62	0.5
r^c	0.994	0.998	0.960	0.954	0.992	0.999

[a] Number of experimental values.

[b] Standard deviation in ppb.

[c] Linear correlation coefficient between experimental and calculated data.

[d] Parameter already contained in B_0.

The ${}^2\Delta$ isotope effects can be described using only two parameters, α- and β-methyl substitution. Whereas for ${}^1\Delta$ isotope effects α-substitution increases the experimental values by about 24 ppb, the opposite is true for ${}^2\Delta$ isotope effects. Reduction by 27 ppb is the average result due to α-substitution. β-Substitution is only of importance for the ${}^2\Delta$ effects, this parameter being close to zero for all other isotope effects.

Thus ${}^3\Delta$ isotope effects can be described using two parameters, α-substitution and the steric correction, $\alpha\beta$, for two adjacent methyl groups. For ${}^3\Delta$ isotope effects, the latter parameter has essentially the same value as found in the analysis of the ${}^1\Delta$ isotope effects. The increment for α-substitution is negative, as calculated for the ${}^2\Delta$ effects. Finally, the B_0 value for the ${}^4\Delta$ isotope effects is essentially zero within the limits of our experimental error; only α- and γ-substitution are important.

There is an interesting and opposite behavior on comparing ${}^1\Delta$ and long-range isotope effects. Whereas a γ-methyl group decreases the ${}^1\Delta$ isotope effect by 7 ppb, it increases the ${}^4\Delta$ effect by about the same value. Thus the statistically derived parameters in Table 2 reveal a large number of internal relationships and consistencies of the isotope effects for the different aromatic carbon atoms.

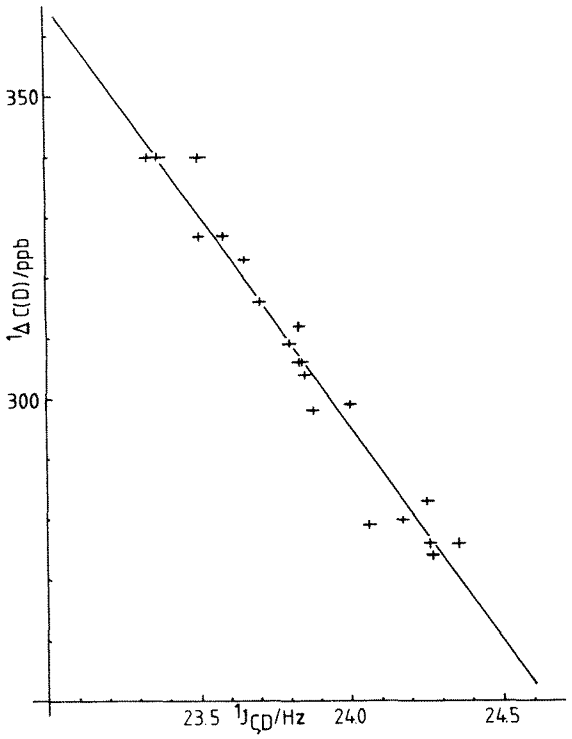


Figure 1. Correlation between $^1\Delta$ deuterium isotope effects and ^1J(CD) spin–spin coupling constants for the methylbenzenes **1**.

The methyl groups can be treated using the same formalism. The basis value B_0, of course, already contains the α- or β-parameters, since isotope effects on methyl groups can only be measured if α- or β-methyl groups are present. The $^3\Delta$ isotope effect is enhanced if further steric congestion by *ortho* di- or tri-substitution is experienced. The $^4\Delta$ isotope effects on methyl groups can only be detected if α- and β-substitution are present; hence the basis value is zero.

For the interpretation of the results in Tables 1 and 2 it is worth reviewing briefly the current discussion on the nature of intrinsic isotope effects. Their origin was shown to be entirely[9] or at least partly[10] vibrational. However, many aspects have led organic chemists to speak of isotope-induced substituent effects,[2] and the common use of the term hyperconjugation in connection with isotope effects (especially of deuteriated methyl groups) is clearly not in accordance with pure vibrational terms. Ernst *et al.*[10] and Wesener and Günther[11] have shown that a dual mechanism is likely to operate in deuteriomethylated aromatic compounds, the hyperconjugational part being of opposite sign to the pure vibrational contribution.

The validity of our statistical approach is first borne out by the B_0 values in Table 2, which in the third row display well the intrinsic isotope effects of deuteriobenzene (**1a**) itself; thus, all isotope effects of the 20 polymethylated compounds can be incrementally calculated starting from deuteriobenzene.

An analogy with aliphatic compounds can be seen in row 4 of Table 2. Wesener *et al.*[12] have shown that substitution in the β-position with respect to the deuterium increases $^1\Delta$ isotope effects. Similarly a correlation has been established[12] between $^1\Delta$ isotope effects and $'J$(CH), the sign of the slope being negative.

For the methylbenzenes given here this is again demonstrated in Fig. 1 for $^1\Delta$ isotope effects and ^1J(CD) spin coupling constants, from which ^1J(CH) spin coupling constants can be calculated by multiplication with a constant factor.[5] Since ^1J(CH) values correlate with the s-character of the C—H bond,[5] the sign of the slope in Fig. 1 is at first sight difficult to understand.[12] In row 6 of Table 2 it can be seen that methyl substitution in the *para*-position with respect to the deuterium atom decreases the $^1\Delta$ isotope effect. For 11 other substituents in the *para* -position to the deuterium we have shown[13] that the $^1\Delta$ isotope effects obey a Hammett relationship, where substituents with $+M$ effects decrease the $^1\Delta$ isotope effect. Such a correlation was first tried by Bell *et al.*[14]; however, our data differ significantly from this early work.

All these findings can be interpreted to the extent that substituents which increase the electron density at the deuteriated carbon atom decrease the $^1\Delta$ isotope effect. $^1\Delta$ isotope effects reflect the change on going from a C—H bond to a C—D bond. If a C—H bond is already polarized by electron release of a substituent, the relative isotope effect, $\Delta^1\Delta$, for this bond could, indeed, be negative. It is interesting to note within this context that $^1\Delta$ isotope effects of compounds **1** correlate with $^2\Delta$ isotope effects, although the relative changes $\Delta^1\Delta$ are of opposite sign to $\Delta^2\Delta$.

CONCLUSION

We have shown that deuterium isotope effects in all monodeuteriated methylbenzenes show incremental behaviour. They can be described quantitatively by the formalism developed for the substituent dependence of chemical shifts,[15] and there is a correlation between C,H spin coupling constants and $^1\Delta$ isotope effects. Hence all these values can be interpreted within the framework of substituent-induced changes in a molecule.

EXPERIMENTAL

All deuteriated compounds were prepared from the corresponding brominated methylbenzenes, which were obtained by standard literature procedures if not commerically available. A typical procedure for deuteriation and work-up is outlined below. The corresponding H compounds were obtained commerically. All samples were purified by preparative GLC (90-P3 Aerograph, 1.8 m × 0.25 in i.d. column, 5% SE-30 on Chromosorb G AW DMCS, 60–80 mesh; carrier gas, helium, flow-rate 120–130 m min^{-1}. n-Butyllithium was purchased from Aldrich.)

Standard Procedure for Deuteriation of Bromomethylbenzenes

A two-necked flask equipped with a stirring bar was flame-dried under nitrogen and closed with a rubber septum. The flask was charged with 10 ml of anhydrous tetrahydrofuran and 5 mmol bromobenzene derivative. With stirring, the solution was cooled to −78 °C by means of a dry-ice–acetone bath. *n*-Butyllithium (3.7 ml, 5.5 mmol) in hexane was slowly added. After complete addition, the mixture was stirred for 10 min. The mixture was then allowed to warm up to 0 °C and stirred for 5 min. D_2O (0.5 ml) was added and the yellow solution turned milky. Water was added until dissolution of the precipitate was complete. The reaction mixture was extracted with diethyl ether and the organic phase dried over $MgSO_4$. After evaporation of the solvent, the product was purified by GLC. Deuteriation was usually better than 96% and the yield essentially quantitative.

NMR Measurements

The 100.6 MHz ^{13}C NMR spectra were recorded on a Bruker WH-400 spectrometer equipped with an 80K Aspect 2000 computer using acetone-d_6 solutions, or in some cases $CDCl_3$, with no detectable difference of the deuterium isotope effects. The measurements were performed first with the pure deuteriated compounds and then repeated after subsequent addition of small amounts of the unlabelled material. The spectral width was set to be as narrow as possible and separate for the aromatic and aliphatic regions, typically between 2000 and 4000 Hz. Zero filling to 64K gave a digital resolution of better than 0.1 Hz per point after the Fourier transform. Gaussian multiplication was used to increase the resolution.

The statistical computations were performed on an IBM 4361 computer of the Hochschulrechenzentrum Marburg using the FORTRAN subroutine F04JGF of the NAG Library.

Acknowledgements

This work was supported by the Fonds der Chemischen Industrie and by the Deutsche Forschungsgemeinschaft (Be 631/6-3).

REFERENCES

1. For recent reviews, see P. E. Hansen, *Annu. Rep. NMR Spectrosc.*, edited by G. A. Webb, Academic Press, New York, **15**, 105 (1983); D. A. Forsyth, in *Isotopes in Organic Chemistry*, edited by E. Buncel and C. C. Lee, Vol 6, Chapt. 1. Elsevier, New York (1984).
2. E. A. Halevi, *Progr. Phys. Org. Chem.*, edited by R. W. Taft, Academic Press, New York **1**, 109 (1963), H. Batiz-Hernandez and R. A. Bernheim, *Prog. Nucl. Magn. Reson. Spectrosc.*, edited by J. W. Ernsley, J. Feeney and L. H. Sutcliffe, Pergamon Press, Oxford, **3**, 63 (1967).
3. H. Künzer and S. Berger, *J. Am. Chem. Soc.* **107**, 2804 (1985).
4. H. Künzer and S. Berger, *Tetrahedron Lett.* 5019 (1984).
5. H. O. Kalinowski, S. Berger and S. Braun, *^{13}C-NMR Spektroskopie*, pp. 92*ff.* Georg Thieme, Stuttgart (1984).
6. P. E. Hansen, F. M. Nicolaisen and K. Schaumburg, *J. Am. Chem. Soc.* **108**, 625 (1986).
7. D. K. Dalling, K. H. Ladner, D. M. Grant and W. R. Woolfenden, *J. Am. Chem. Soc.* **99**, 7142 (1977).
8. W. R. Woolfenden, PhD Thesis, University of Utah, (1965); abstracted by J. B. Stothers, *Carbon-13 NMR Spectroscopy*, pp. 94–99. Academic Press, New York (1972).
9. C. J. Jameson, *J. Chem. Phys.* **66**, 4983 (1977).
10. L. Ernst, H. Hopf and D. Wullbrandt, *J. Am. Chem. Soc.* **105**, 4469 (1983).
11. J. R. Wesener and H. Günther, *Tetrahedron Lett.* 2845 (1982).
12. J. R. Wesener, D. Moskau and H. Günther, *J. Am. Chem. Soc.* **107**, 7307 (1985).
13. S. Berger and B. W. K. Diehl, in preparation
14. R. A. Bell, C. L. Chan and G. G. Sayer, *J. Chem. Soc., Chem. Commun.* 67 (1972).
15. C. J. Jameson, *Specialist Periodical Reports on NMR*, Vol. 10, p. 1. Chemical Society, London (1981).