ORGANIC LETTERS

2000
Vol. 2, No. 25
4111−4113

Deuterium Isotope Effects on ^{13}C NMR Chemical Shifts Reflect the Smaller Steric Size of CD_3 Compared to CH_3 Groups§

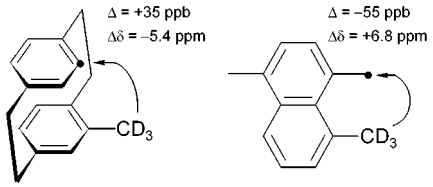
Kerstin Ibrom, Gunther Kohn (né Wentzel), Kai-Uwe Boeckmann, Roswitha Kraft, Petra Holba-Schulz, and Ludger Ernst*

Institut für Organische Chemie, Technische Universität Braunschweig, Hagenring 30, D-38106 Braunschweig, Germany

l.ernst@tu-bs.de

Received October 26, 2000

ABSTRACT



A CD_3 group close in space to (but many bonds distant from) a carbon atom A causes a substituent effect on the chemical shift of C_A that is algebraically smaller than the effect of a CH_3 group, in agreement with the notion of shorter C–D relative to C–H bonds. Hence, the deuterium isotope effect of CD_3 upon $\delta(C_A)$ is shielding when the substituent effect is deshielding, and vice versa.

Isotope effects on chemical shifts[1] are very useful in the analysis of the NMR spectra of labeled compounds and thus of great value in the elucidation of chemical or biological processes. They are also interesting in their own right, and much work has been performed to advance their understanding.[2] It is customary to distinguish equilibrium isotope effects[2d] from intrinsic isotope effects.[3] Whereas the former are due to changes of the populations of chemically or conformationally equilibrating species as a consequence of the isotopic replacement, the latter are inherent to a single molecular species and are brought about by changes in the rovibrational averaging of all electronic properties of the molecule caused by the mass change.

Intrinsic isotope effects acting over more than three bonds are usually negligible in saturated systems, but effects over up to 12 bonds have been observed in conjugated π systems.[4] Such long-range effects often correlate with other purely electronic quantities that are dependent on the same electronic transmission path, e.g., substituent effects on chemical shifts.[2i] Intrinsic steric isotope effects of deuterium upon the chemical shifts of protons close in space were reported by Anet and Dekmezian.[5] These authors postulated that such

§ This paper is dedicated to Professor Henning Hopf on the occasion of his 60th birthday.

(1) We define isotope effects on chemical shifts as $\Delta = \delta$(heavy isotopomer) minus δ(light isotopomer), e.g., $\Delta = \delta(R-D) - \delta(R-H)$. The opposite sign convention is also found in the literature. Isotope effects are given in ppb because of their smallness (1 ppm = 1000 ppb).

(2) For reviews, see: (a) Batiz-Hernandez, H.; Bernheim, R. A. *Prog. NMR Spectrosc.* **1967**, *3*, 63−85. (b) Hansen, P. E. *Annu. Rep. NMR Spectrosc.* **1983**, *15*, 105−234. (c) Forsyth, D. A. In *Isotopes in Organic Chemistry*; Buncel, E., Lee, C. C., Eds.; Elsevier: Amsterdam, 1984; Vol. 6, pp 1−66. (d) Siehl, H.-U. *Adv. Phys. Org. Chem.* **1987**, *23*, 63−163. (e) Jameson, C. J.; Osten, H. J. *Annu. Rep. NMR Spectrosc.* **1986**, *17*, 1−78. (f) Hansen, P. E. *Prog. NMR Spectrosc.* **1988**, *20*, 207−255. (g) Berger, S. *NMR Basic Princip. Prog.* **1990**, *22*, 1−29. (h) Berger, S. In *Encyclopedia of Nuclear Magnetic Resonance*; Grant, D. M., Harris, R. K., Eds.; Wiley: Chichester, 1996; Vol. 2, pp 1168−1172. (i) Jameson, C. J. In *Encyclopedia of Nuclear Magnetic Resonance*; Grant, D. M., Harris, R. K., Eds.; Wiley: Chichester, 1996; Vol. 4, pp 2638−2655. (j) Novak, P.; Vikić-Topić, D.; Smrečki, V.; Meić, Z. In *New Advances in Analytical Chemistry*; Atta-ur-Rahman, Ed.; Gordon and Breach: Amsterdam, in press.

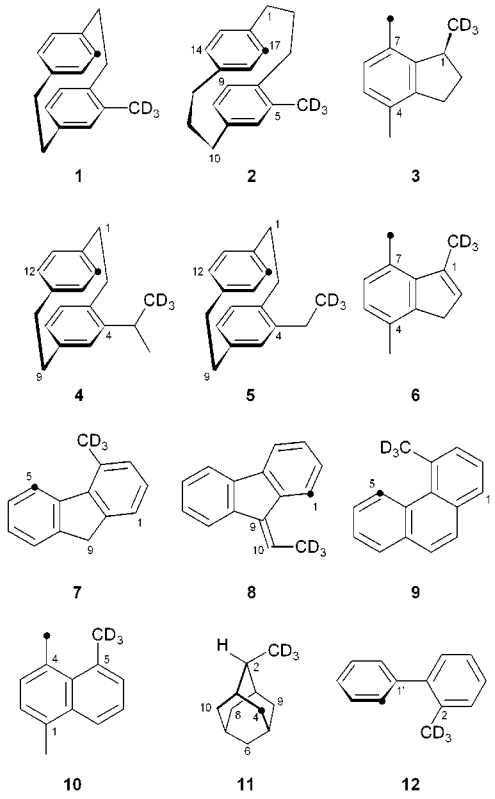
(3) Jameson, C. J. In *Isotopes in the Physical and Biomedical Science*; Buncel, E., Jones, J. R., Eds.; Elsevier: Amsterdam, 1991, Vol. 2, pp 1−54.

(4) Berger, S.; Künzer, H. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 321−322.

10.1021/ol006780y CCC: $19.00
Published on Web 11/15/2000

steric isotope effects should also act upon ^{13}C chemical shifts, but this was not observed. Also later, only scarce reports of such effects appeared,[6−8] while equilibrium isotope effects abound in the literature, in particular those in intramolecularly hydrogen-bonded systems.[9]

We now present a series of compounds, **1**−**12**,[10] which carry a trideuteriomethyl group that is close in space to a C−H bond but in which the deuterons are separated from the affected carbon atom by at least five chemical bonds (in one case by four bonds). Large intrinsic steric isotope effects



of the CD_3 groups upon the chemical shifts of the nearby carbon nuclei are present in this series.[11] Some time ago, serendipity had furnished 4-CD_3-[2.2]paracyclophane (**1**) as the first example.[12] This compound exhibits a large deshielding isotope effect ($\Delta = +35.1$ ppb) on the shift of the pseudogeminal carbon. The deshielding nature of this effect was surprising as the majority of the known deuterium isotope effects on ^{13}C shifts are shielding. The next compound we studied was naphthalene **10** because of the strong interaction expected between the CD_3 and the *peri* methyl group.[13] In this case, the isotope effect turned out also to be large but, surprisingly, of the opposite sign to that of **1**, i.e., it is shielding ($\Delta = -55.2$ ppb). We noticed that an analogy to this sign change of the isotope effect exists in the sign change of the substituent effect, $\Delta\delta$, by which the ^{13}C shift of the site under consideration is changed when the methyl group is introduced into the molecule. In other words, for the carbon sites subject to steric interaction we compare the isotope effects $\Delta = \delta(R-CD_3) - \delta(R-CH_3)$ with the methyl substituent effects $\Delta\delta = \delta(R-CH_3) - \delta(R-H)$. The latter are −5.40 and +6.82 ppm for **1** and **10**, respectively.

We then investigated the other compounds of the series **1**−**12**, in which both shielding and deshielding steric substituent effects on ^{13}C shifts are present. (The affected carbon atoms are marked with a "•" sign in the formulas.) We found that large negative substituent effects go along with large positive isotope effects and vice versa (Table 1).

Table 1. Methyl Substituent Effects ($\Delta\delta^a$) and CD_3 Isotope Effects (Δ^b) on the Chemical Shifts of Spatially Close Carbon Sites[c] in **1**−**12**

compound	$\Delta\delta$ [ppm]	Δ [ppb]
1	−5.40	35.1
2	−3.05	20 ± 1
3	−0.54	−2.3
4	1.00	−12.3[d]
5	1.05	−12.7
6	1.27	−23.0
7	3.31	−33.2
8	3.96	−32.7
9	4.79	−35.5
10	6.82	−55.2
11	−6.51	24.3
12	2.03	−4.2

[a] $\Delta\delta = \delta(R-CH_3) - \delta(R-H)$. [b] $\Delta = \delta(R-CD_3) - \delta(R-CH_3)$. [c] These are marked with a "•" sign in formulas **1**−**12**. [d] Average of the individual values (−9.3 and −15.3 ppb) for the two diastereotopic CD_3 groups.

The plot of Δ[ppb] vs $\Delta\delta$[ppm] (Figure 1) shows that, for compounds **1**−**10**, the data obey a linear equation (eq 1) with a correlation coefficient r of 0.991.

$$\Delta = -7.3\Delta\delta - 5.5 \qquad (1)$$

The data points for **11** and **12** are farthest off the line and were not included in the data set from which eq 1 was

(5) Anet, F. A. L.; Dekmezian, A. H. *J. Am. Chem. Soc.* **1979**, *101*, 5449−5451.

(6) For steric effects of a single deuteron upon the chemical shifts of vicinal or ortho carbon nuclei, see: (a) Jurlina, J. L.; Stothers, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 4677−4678. (b) Berger, S.; Diehl, B. W. K. *Magn. Reson. Chem.* **1986**, *24*, 1073−1076.

(7) For steric effects of deuterons upon ^1H chemical shifts, see: Biali, S. E.; Rappoport, Z.; Hull, W. E. *J. Am. Chem. Soc.* **1985**, *107*, 5450−5459.

(8) For steric effects of deuterons upon ^{19}F chemical shifts, see: (a) Young, W. R.; Yannoni, C. S. *J. Am. Chem. Soc.* **1969**, *91*, 4581−4582. (b) Hansen, P. E.; Bolvig, S.; Buvari-Barcza, A.; Lycka, A. *Acta Chem. Scand.* **1997**, *51*, 881−888.

(9) Hansen, P. E. *Curr. Org. Chem.* **2000**, *4*, 19−54 and references therein.

(10) The nondeuterated analogues of **1**−**12** are all known compounds. The analogues of **1**−**5** and of **7**−**12** are contained in the Beilstein database. For the analogue of **6**, see: Goutines, G.; Mathieu, A. *Analusis* **1973**, *2*, 584−589.

(11) Deuterium isotope effects on ^{13}C chemical shifts were determined at 101 MHz observation frequency from mixtures of the CD_3 and CH_3 compounds in $CDCl_3$. To verify the signs of the effects, at least two mixtures of different CD_3/CH_3 ratio were prepared for each compound. Digital resolutions employed were 1 ppb (0.1 Hz) per data point or better.

(12) Ernst, L.; Eltamany, S.; Hopf, H. *J. Am. Chem. Soc.* **1982**, *104*, 299−300.

(13) The additional methyl group in **10** serves to render the molecule more unsymmetrical because it is usually difficult to assign the NMR spectra of molecules that are unsymmetrical only as a result of the presence of isotopes.

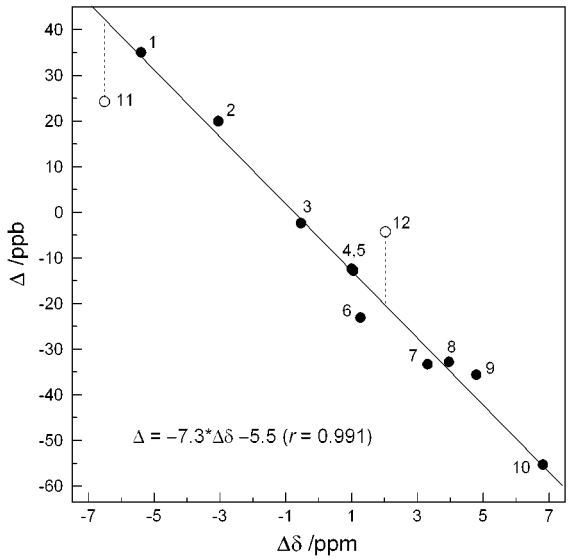


Figure 1. Plot of the CD_3 isotope effects (Δ) vs the CH_3 substituent effects ($\Delta\delta$) on the chemical shifts of spatially close carbon nuclei. Only data points 1−10 were considered in deriving the least squares line. The data point numbers correspond to the compound numbers.

derived. The outlying data point of adamantane **11** is in line with the conclusion by Aydin et al. that the isotope effects of axial CD_3 groups upon δ(C-3) in different 1-CD_3-cyclohexanols are not purely due to spatial proximity.[14] The reason for the deviation of the data point of biphenyl **12** from the trend of the others is not clear at present, and we refrain from speculating on this matter.

Although much progress has been made recently in experimentally determining ^{13}C chemical shift tensors[15] and in calculating the conformational dependencies of isotropic ^{13}C chemical shifts,[16] it is still not easy to understand why steric substituent effects of methyl groups are so strongly shielding in some cases (especially in **1**, **2**, and **11**) and so strongly deshielding in others such as **7**−**10**. Our data show that no matter whether a steric methyl substituent effect is shielding or deshielding, the effect of a CD_3 group is always algebraically smaller than that of a CH_3 group. This makes the isotope effect (which is identical[17] to the difference between the substituent effects of CD_3 and CH_3) shielding when the substituent effect is deshielding and vice versa. This behavior is in accord with the notion of slightly shorter C−D bonds with respect to C−H bonds. The bond length difference is of the order of 0.5 pm.[18] Also, the smaller amplitudes of the C−D stretching and bending motion relative to C−H can be regarded as if deuterium had a slightly smaller van der Waals radius than hydrogen (149.7 compared to 150.0 pm). Thus, molecular mechanics calculations, which are parametrized accordingly, predict less severe nonbonded interactions of deuterium-containing groups than of their protium analogues.[19] The smaller nonbonded interactions should lead to lesser NMR substituent effects. This is indeed what the above experiments have shown.

In short, isotope effects of CD_3 groups on the chemical shifts of spatially close (but many bonds distant) carbon nuclei can be explained by the smaller steric size of CD_3 relative to CH_3 groups. This leads to algebraically smaller substituent effects of the former with respect to the latter groups and, hence, to the opposite sign of substituent and isotope effects.

Acknowledgment. We thank Professor Henning Hopf for making available the facilities of his group and of the Institute of Organic Chemistry. This work was partly supported by the Fonds der Chemischen Industrie, Frankfurt/Main, Germany.

Supporting Information Available: ^1H and ^{13}C NMR data for the protium isotopomers of compounds **1**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL006780Y

(14) Aydin, R.; Wesener, J. R.; Günther, H.; Santillan, R. L.; Garibay, M.-E.; Joseph-Nathan, P. *J. Org. Chem.* **1984**, *49*, 3845−3847.
(15) See, e. g., Harper, J. K.; McGeorge, G.; Grant, D. M. *Magn. Reson. Chem.* **1998**, *36*, S135−S144.
(16) Barfield, M. *Magn. Reson. Chem.* **1998**, *36*, S93−S103.
(17) The substituent effects on chemical shifts exerted by a CD_3 and by a CH_3 group are defined as $\Delta\delta(CD_3) = \delta(R-CD_3) - \delta(R-H)$ and $\Delta\delta(CH_3) = \delta(R-CH_3) - \delta(R-H)$, respectively. Subtraction gives $\Delta\delta(CD_3) - \Delta\delta(CH_3) = \delta(R-CD_3) - \delta(R-CH_3)$. This equals Δ, the isotope effect of a CD_3 group.
(18) Bartell, L. S.; Higginbotham, H. K. *J. Chem. Phys.* **1965**, *42*, 851−856.
(19) Allinger, N. L.; Flanagan, H. L. *J. Comput. Chem.* **1983**, *4*, 399−403.