Pergamon

Tetrahedron Letters 39 (1998) 4191–4194

TETRAHEDRON
LETTERS

Investigations Utilizing the ^{18}O Isotope Shift in ^{13}C Nuclear Magnetic Resonance Spectroscopy. 3. Observation of a Solvent Dependence for *tert*-Butyl Alcohol[1]

Laurie J. Hasbrouck and John M. Risley*

Department of Chemistry, The University of North Carolina at Charlotte, Charlotte, North Carolina 28223-0001, USA

Received 19 February 1998; accepted 30 March 1998

Abstract: Solvent effects on the magnitude of the ^{18}O isotope shift in ^{13}C NMR for the carbon bonded to the hydroxyl group in *tert*-butyl alcohol were investigated using an array of deuterated solvents and a more accurate measurement of the isotope shift at natural abundance ^{13}C. For the first time, a solvent effect on the magnitude of the isotope shift was detected, which was smallest in pyridine, and increased in the following order: pyridine < acetone/*p*-dioxane < nitromethane < benzene < water. These results indicate that assignments of carbon signals based on the magnitude of isotope shifts must take into account the possibility of a solvent effect.

INTRODUCTION

Oxygen-18 isotope shifts in ^{13}C NMR spectroscopy have been widely used in a variety of mechanistic studies (*e.g.*, oxygen exchange reactions, point of bond cleavage, inorganic chemistry mechanisms, organic chemistry, enzyme mechanisms) and in biosynthetic studies (*e.g.*, origin of the oxygen in natural products).[2] The properties of the isotope shifts have been studied extensively.[2] The magnitudes of the ^{18}O isotope shifts in ^{13}C NMR for nearly all of the compounds have been reported in only one solvent, generally either deuterium oxide (or water/deuterium oxide mixtures) or chloroform-*d*.[2] In the few studies of the shifts in various solvents, only negligible solvent effects, if any, have been observed.[2] These observations contrast with the significant solvent effects for oximes seen in the ^{18}O isotope shifts in ^{15}N NMR spectroscopy.[2] We thought that is was likely that there could be solvent effects on the ^{18}O isotope shift in ^{13}C NMR that may be detectable. Therefore, we have investigated the question of solvent effects on the magnitude of the ^{18}O isotope shift in natural abundance ^{13}C NMR for the hydroxyl carbon in [^{18}O]*tert*-butyl alcohol in an array of solvents because the hydroxyl carbon has a large isotope shift that may be more sensitive to a change in solvents.

EXPERIMENTAL

[^{18}O]Water (95 + atom % ^{18}O, normalized, EG & G Mound), deuterium oxide (99.9 atom % ^{2}H,

PII: S0040-4039(98)00782-5

Sigma), and pyridine-d_5, acetone-d_6, *p*-dioxane-d_8, nitromethane-d_3, and benzene-d_6 (CIL) were used in the study. All other reagents were analytical or spectrometric grade. [^{18}O]*tert*-Butyl alcohol was synthesized and purified as previously described.[3] The ^{18}O content was 35% as determined by the ^{18}O isotope shift in ^{13}C NMR.[4]

Natural abundance ^{13}C NMR spectra were recorded on a GE-300 spectrometer operating at 75.5 MHz at ambient temperature (4000-Hz sweep width, 90° pulse angle, 65K data block, and protons broad-band decoupled) to a final resolution of 8 points/Hz; a line-broadening factor was applied to the FID. The concentration of the alcohol in each solvent was less than 100 mM. The error in the measured isotope shift was ±0.8 ppb (parts per billion).

RESULTS AND DISCUSSION

The natural abundance ^{13}C NMR signal for the hydroxyl carbon in [^{18}O]*tert*-butyl alcohol in three of the solvents is shown in Fig. 1. The ^{18}O isotope induces an upfield shift in the ^{13}C NMR signal that is well resolved.[5] The smallest isotope shift of 26.6 ppb is observed in pyridine-d_5 (Fig. 1A), a mid-range isotope shift of 29.0 ppb is observed in acetone-d_6 (Fig. 1B), and the largest isotope shift of 35.0 ppb is observed in deuterium oxide (Fig. 1C). The ^{18}O isotope shift for the hydroxyl carbon in [^{18}O]*tert*-butyl alcohol at natural abundance ^{13}C in the six different solvents used in this study is given in ppb upfield in Table 1. These are the

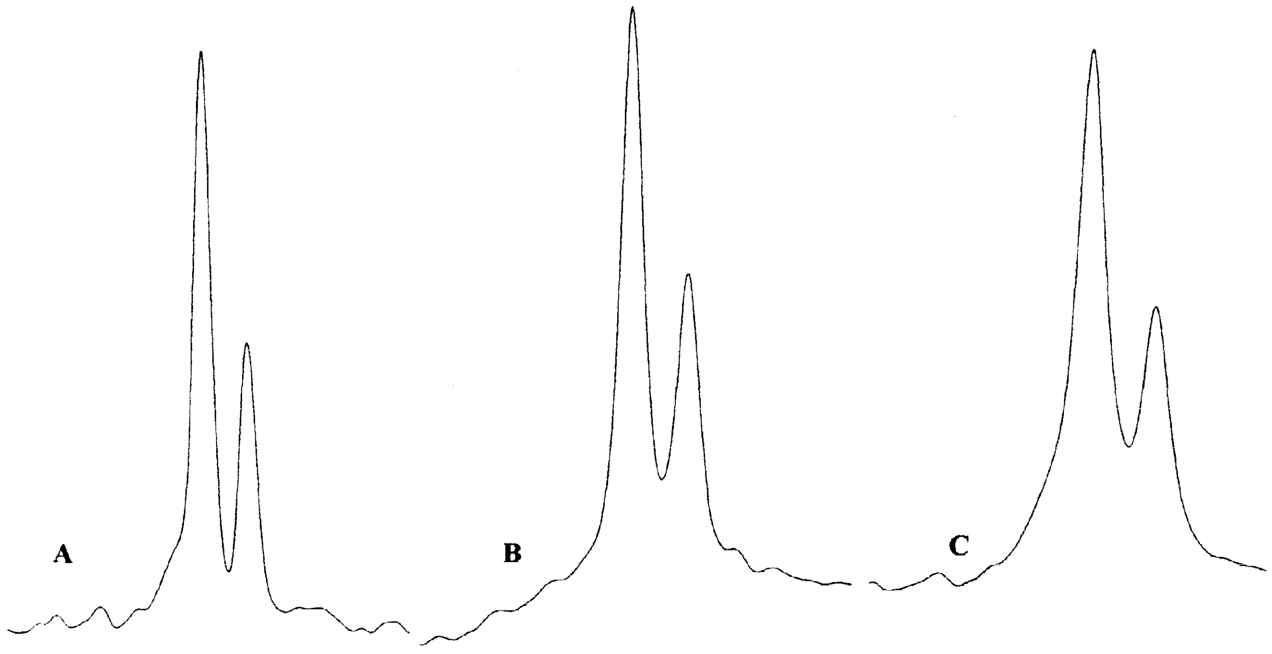

Fig. 1. The ^{18}O isotope-induced shift for the ^{13}C NMR signal of the hydroxyl carbon in [^{18}O]*tert*-butyl alcohol in upfield (A) 26.6 ppb in pyridine-d_5, (B) 29.0 ppb in acetone-d_6, and (C) 35.0 ppb in deuterium oxide. The ^{18}O content is 35%.

Table 1. ^{18}O Isotope Shift for the ^{13}C NMR Signal of the Hydroxyl Carbon in [^{18}O]*tert*-Butyl Alcohol

Solvent:	pyridine-d_5	acetone-d_6	*p*-dioxane-d_8	nitromethane-d_3	benzene-d_6	water-d_2
Isotope Shift (ppb):	26.6	29.0	29.1	29.9	30.7	35.0

most accurate isotope shifts measured as a function of solvent that have been reported for this alcohol. There is a significant increase in the magnitude of the isotope shift as the solvent is changed from pyridine-d_5 to acetone-d_6/*p*-dioxane-d_8 to nitromethane-d_3 to benzene-d_6 to deuterium oxide.

The solvent dependence on isotope shifts in NMR has not been widely reported.[2,6] A few studies of a solvent dependence on the ^{18}O isotope shift in ^{13}C NMR have been reported. The magnitude of the isotope shift in primary alcohols is 18-21 ppb whether in H_2O/D_2O or $CDCl_3$; for example, the isotope shift of the hydroxyl carbon in benzyl alcohol is 19±1 ppb in both 20% D_2O and $CDCl_3$.[2] In secondary alcohols, the magnitude of the isotope shift is 23-26 ppb whether in D_2O or $CDCl_3$;[2] however, the hydroxyl carbon in 1-phenylethanol shows a small solvent effect in pyridine-d_5 (20±1 ppb), benzene-d_6 (21±1 ppb), and $CDCl_3$ (23±1 ppb).[7] In tertiary alcohols, the magnitude of the isotope shift is 30-35 ppb whether in D_2O, acetone-d_6, or $CDCl_3$;[2] however, the hydroxyl carbons in 2-cyclohexyl-2-propanol (32±1 ppb) and 1-methylcyclohexanol (31.2±0.6 ppb) show isotope shifts in $CDCl_3$[7,8] marginally greater than in benzene-d_6 observed in this study (30.7 ppb). The isotope shifts for the carbonyl carbon in acetone and for the carboxyl carbon in benzoic acid are the same in both $CDCl_3$ and D_2O.[2] The isotope shifts for the carboxyl carbons in the monoanions of dicarboxylic acids are the same in THF-d_8, Me_2SO-d_6, CD_3CN, $CDCl_3$, CD_2Cl_2, and D_2O.[9,10] Finally, the isotope shift for the carboxyl carbon in n-propyl [*carbonyl*-^{18}O]benzoate (33±1 ppb) is identical in pyridine-d_5, Me_2SO-d_6, benzene-d_6, $CDCl_3$, and methanol-d_4.[7]

In other studies, the ^{2}H isotope shifts in ^{13}C NMR for hydroxyl groups in deuterated sugars are greater in D_2O than in Me_2SO-d_6,[11] while in *o*-hydroxyacetophenone the isotope shift is identical in $CDCl_3$ and Me_2SO-d_6.[6] Also, the ^{18}O isotope shift in ^{15}N NMR for oximes shows a significant solvent dependence where the magnitude of the isotope shift increases as the solvent is changed from pyridine-d_5 to Me_2SO-d_6/$CDCl_3$ (1:4, v:v)/THF-d_8 to CD_3CN to $CDCl_3$/benzene-d_6.[12] Finally, while the ^{18}O isotope shift in ^{13}C NMR shows a correlation with ^{17}O NMR chemical shifts,[13] there are apparently no solvent dependence studies on ^{17}O NMR chemical shifts with which to compare our results.[14]

Our data for a solvent dependence on the ^{18}O isotope shift in ^{13}C NMR for the hydroxyl carbon in [^{18}O]*tert*-butyl alcohol are consistent with the observations for 1-phenylethanol, 2-cyclohexyl-2-propanol, 1-methylcyclohexanol, deuterated sugars, and oximes outline above. Taken together, these data indicate a general trend for solvent effects on the magnitude of the ^{18}O isotope shifts in compounds containing a hydroxyl group as increasing in the following order: pyridine < THF/Me_2SO < CH_3CN < acetone/*p*-dioxane < CH_3NO_2 < benzene/$CHCl_3$ < H_2O. An interesting point is that this general trend for solvent effects appears to correlate with no known physical parameter of the solvents, such as dielectric constant, dipole moment, polarizability, H-bonding, pK_a, etc.[15] However, a model has been described that provides a mechanism for nonspecific solvent effects on NMR isotope shifts that involves site factors.[16] The model expectation is that the solvent effects on isotope shifts in NMR are generally small because the differences in site factors for two isotopomers are small for most isotopic substitutions. The data presented in this study support the expectation of the model. The solvent effect on the isotope shift for the hydroxyl carbon in *tert*-butyl alcohol is ≤8.4 ppb, while the solvent effect on the isotope shift for the oxime nitrogen in oximes is ≤16 ppb. In those instances where no solvent effect was observed, it may be that the magnitude of the solvent dependence is so small that it has not yet been detected.[17] However, these results indicate that care must be exercised in the utilization of the magnitudes of isotope shifts to make assignments of carbon signals due to the possibility of a solvent effect. We are not aware at this time of an error in the assignment of a carbon signal based on the magnitude of an observed isotope shift due to a solvent effect, but the results that we have reported here require caution in the selection of solvents for the measurement of isotope shifts.

ACKNOWLEDGEMENTS

This research was supported by a Cottrell College Science Award of Research Corporation and, in part, by funds provided by the University of North Carolina at Charlotte.

REFERENCES AND NOTES

1. Part 2: Arias, W.; Risley, J. M. *J. Org. Chem.* **1991**, *56*, 3741-3744.
2. Risley, J. M.; Van Etten, R. L. *NMR Basic Princ. Prog.* **1990**, *22*, 81-168.
3. Risley, J. M.; Van Etten, R. L. *J. Am. Chem. Soc.* **1979**, *101*, 252-253.
4. Risley, J. M.; Van Etten, R. L. *Methods Enzymol.* **1989**, *177*, 376-389.
5. The apparent increase in peak widths with isotope shifts in the three solvents shown is not a general observation. Because the ^{13}C NMR spectra were recorded at various times in the different solvents, and because the magnitudes of these isotope shifts are small, variations in peak widths can occur with minor differences in shim adjustments on the NMR and can also arise from using NMR tubes that are slightly different; however, the magnitudes of the isotope shifts are not affected by either of these.
6. Hansen, P. E. *Prog. NMR Spectrosc.* **1988**, *20*, 207-255.
7. Vederas, J. C. *J. Am. Chem. Soc.* **1980**, *102*, 374-376.
8. Diakur, J.; Nakashima, T. T.; Vederas, J. C. *Can. J. Chem.* **1980**, *58*, 1311-1315.
9. Perrin, C. L.; Thoburn, J. D. *J. Am. Chem. Soc.* **1992**, *114*, 8559-8565.
10. Perrin, C. L.; Nielson, J. B. *J. Am. Chem. Soc.* **1997**, *119*, 12734-12741.
11. Reuben, J. *J. Am. Chem. Soc.* **1983**, *105*, 3711-3713.
12. Rajendran, G.; Santini, R. E.; Van Etten, R. L. *J. Am. Chem. Soc.* **1987**, *109*, 4357-4362.
13. Risley, J. M. *Magn. Reson. Chem.* **1991**, *29*, 143-147.
14. Boykin, D. W., editor. *^{17}O NMR Spectroscopy in Organic Chemistry*; CRC Press: Boca Raton, 1991.
15. Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*; Harper & Row: New York, 1976.
16. Jameson, C. J.; Jameson, A. K.; Oppusunggu, D. *J. Chem. Phys.* **1984**, *81*, 2313-2317.
17. A referee suggested that, while the changes in the magnitudes of the isotope shifts do not appear to correlate with any solvation parameter, the differences in the magnitudes of the isotope shifts in the various solvents may be correlated with hydrogen bonding. No study has been reported on the concentration dependence, if any, of the ^{18}O isotope shift in ^{13}C NMR; however, the isotope shift for the hydroxyl carbon in [^{18}O]*tert*-butyl alcohol is 35.0 ppb in H_2O/D_2O at 1.88 M [3] and at ≤ 0.1 M (this study). One study[18] has been reported for *tert*-butyl alcohol on the chemical shift of the proton and hydrogen bonding in 12 inert and proton-acceptor solvents; only three solvents (acetone, dioxane, and nitromethane) are the same in both studies. Unfortunately, there are insufficient data to draw any conclusions at the moment. However, if the proton chemical (association) shift for *tert*-butyl alcohol is comparable to that of phenol in pyridine, acetone, dioxane, and benzene,[19] then a correlation would be strongly indicated. It has been shown that the magnitude of the ^{18}O isotope shift for carbonyl carbons is decreased upon intramolecular hydrogen bonding in *o*-hydroxyl aromatic ketones,[20] and therefore hydrogen bonding has been shown to affect ^{18}O isotope shifts in ^{13}C NMR. There is sufficient circumstantial evidence to indicate that this possible correlation is worth pursuing.
18. Lemanceau, B.; Lussan, C.; Souty, N. *J. Chim. Phys.* **1962**, *59*, 148-153.
19. Granacher, I. *Helv. Phys. Acta* **1961**, *34*, 272-302.
20. Hansen, P. E.; Ibsen, S. N.; Kristensen, T.; Bolvig, S. *Magn. Reson. Chem.* **1994**, *32*, 399-408.