An Application of ${}^{n}J(CH_{2},H)$ and ${}^{5}J(OH,H)$ Long-Range Couplings in the Conformational Analysis of 2-Hydroxybenzyl Methyl Ether in Various Solvents. Computational Strategies for Spectral Analysis and Determination of Association Thermodynamic Parameters

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¹H NMR spectra of 2-hydroxy- and 2-methoxy-benzyl methyl ethers were measured in various solvents and solvent mixtures. Precise ${}^{n}J(CH_{2},H)$, where n = 4, 5 or 6, and ${}^{5}J(OH,H)$ long-range couplings were applied to the characterization of the conformational behaviour of the systems. Qualitatively, the compounds appear to exist in two principal conformations: in a closed *syn* with an internal hydrogen-bonded form, and/or in an open *anti* conformation with the CH₂OR group tilting fairly freely in the benzene plane. The open form is favoured in acetone and dioxane. The computational strategies used in the spectral analysis of the long-range couplings and in the analysis of the solvent-solute association equilibria are described.

KEY WORDS Conformational Analysis Spin-Spin couplings Analysis of NMR spectra Thermodynamic parameters 2-Hydroxybenzyl methyl ether

INTRODUCTION

The side-chain rotation barrier of benzyl alcohol is obviously small. STO-3G ab initio calculations suggest that the C—O bond prefers to be in the benzene plane to the extent of $0.9 \text{ kJ} \text{ mol}^{-1}$. ¹ Application of the J method² gives $1.2(\pm 0.8) \text{ kJ} \text{ mol}^{-1}$ for 3,5-dichloro-benzyl alcohol.³ For the isoelectronic benzyl fluoride a conformation with a low energy minimum at a dihedral angle of 54° has been reported.⁴ In 2-hydroxybenzyl methyl ether the CH₂OCH₃ group can be thought of as being anchored by a hydrogen bond in a relatively rigid 'closed' conformer, 1A. In the analogous 2-mercaptobenzylmethyl ether only a weak hydrogen bond has been reported.⁵ The purpose of this study was to characterize the conformational behaviour of the system under various solvent conditions, and to test some computer programs developed for this type of problem. The strategies for spectral analysis of small couplings and solvent-solute association equilibria are described and discussed.



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0749–1581/86/070588–07\$05.00 © 1986 by John Wiley & Sons, Ltd. The characterization is based on the well known conformational behaviour of ${}^{n}J(CH_{2},H)$ and ${}^{5}J(OH,H)$ long-range spin-spin couplings. ${}^{6}J(CH,H)$ is proportional to $\langle \sin^{2}\theta \rangle$, where θ is the angle by which the C—H bond is twisted out of the benzene plane.² ${}^{6}J(CH_{2},H)$ has been previously used in the estimation of the rotational freedom of some symmetrical benzyl derivatives.^{2,3,6} The conformational behaviour of ${}^{5}J(CH,H)$ has also been characterized theoretically and experimentally.^{7,8} Both ${}^{5}J(CH_{2},H)$ and ${}^{5}J(OH,H)$ can be used to estimate the *trans-cis* isomerism of the side-chains. Quantitative deductions based on ${}^{5}J(CH_{2},H)$ have not been previously made, but ${}^{5}J(OH,H)$ has been extensively applied in phenols.⁹ The behaviour of ${}^{4}J(CH_{2},H)$ resembles that of ${}^{6}J(CH_{2},H)$, but is more complex¹⁰ and is not quantitatively used in this study.

EXPERIMENTAL

Synthesis

The THF solution of the disodium salt of 2-hydroxybenzyl alcohol (3) for methylation was prepared by the slow addition of 0.05 mol of 3 in 30 ml of THF into a suspension of 0.15 mol of NaH in 200 ml of THF. The reaction mixture was stirred vigorously and maintained at room temperature. Inefficient stirring or too efficient cooling resulted in a thick slurry

> Received 3 August 1985 Accepted (revised) October 1985

containing small hydrogen bubbles. If **1** was desired, 0.05 mol of *n*-BuOH was added in THF and the reaction was allowed to proceed until no more hydrogen was produced; 0.07 mol of CH₃I in 30 ml of THF was added (slowly, 1 h) to the reaction mixture and the reaction allowed to proceed for 3 h. An NMR analysis of the crude product suggested a 70% yield of **1**.

Samples, spectral measurements and calculations

To stop the exchange of the OH protons the solutions were stored overnight over molecular sieves. For measurements with a Bruker WH-90 spectrometer the solutions were filtered before sealing the tube. The proton exchange of **1** in acetone solution was concentration dependent and sometimes difficult to stop. For this reason, dilute (0.5% w/v) solutions were used. All samples were degassed by the freezepump-thaw procedure and were then flame-sealed.

The ¹H NMR spectra of **1** and **2** were obtained on a Bruker WH-90 or a Varian HA-100 CW spectrometer as previously described.¹¹ The proton-coupled ¹³C NMR spectra of **1** and benzyl methyl ether were recorded on a Bruker WH-90 spectrometer.

The calculations were performed on an Amdahl 470/V7 computer of the University of Manitoba and a Vax 11/780 computer of the University of Kuopio, Finland.

RESULTS AND DISCUSSION

Selective methylation of 2-hydroxybenzyl alcohol

Compound 1 was prepared from 2-hydroxybenzyl alcohol (3) by the NaH–CH₃I method (see above). It can also be prepared by the carbonium ion mechanism or through reaction of the diacetate of 3.¹²

Selective methylation of the benzylhydroxy group of 3 occurs when CH₃I is introduced into a THF solution of the disodium salt of 3 in the presence of a buffering alkoxide; this reacts less easily than CH₂ONa but more easily than the phenoxide. The reaction between CH₃I and CH_2ONa is activated by the phenoxide at the ortho position, and takes place much faster than between CH_3I and, for example, an *n*-butoxide buffer. The resonance-stabilized sodium salt of 1 is less reactive than the n-alkoxide, and any excess CH₃I reacts with the *n*-alkoxide. By using the alkoxide the accurate determination of the starting amount of 3 can be avoided. The technique can also be used to prevent the formation of the disodium salt of 3: the phenolic hydroxy group of 3 can be selectively methylated in the presence of excess of CH_3I . The dimethyl ether 2 can be prepared from the disodium salt of 3 by using CH₃I in excess.

Spectral analysis: an automatical assignment procedure

The ring proton spectra were tightly coupled and rather complex (Fig. 1). They were analysed with the



Figure 1. H-4 and H-6 regions for 0.5% v/v solutions of 2-methoxybenzyl methyl ether in CS₂ (above) and 2-hydroxybenzyl methyl ether in 10% acetone- d_6 in CCl₄ (below) at 90 MHz and 305 K. The lower spectrum shows the splittings of 0.383 and 0.176 Hz to the hydroxy proton.

MAOCON program,^{13,14} which contains an automatic assignment procedure. After a few spectral lines have been assigned with certainty and the trial parameters have been optimized with respect to these lines, the program assigns and reassigns observed signals during the following iterative procedure. The observed signal nearest to the calculated frequency is chosen to represent a theoretical line and if the difference between the observed and calculated frequencies is unreasonable [twice the residual root mean square (rrms)], the assignment is not used in the following cycle for the optimization of the spectral parameters. A typical number of assigning and reassigning cycles was 5–10.

The traditional practice with overlapping lines is either to assign all the nearly degenerate lines to the same observed signal or to assign only the most intense and representative lines. The procedure usually leads to many errors and ambiguous solutions, and is also tiresome. In the case of a near degeneracy of the lines, the procedure can lead to large systematic errors in the couplings. We have found¹⁵ that a spectrum cannot always be satisfactorily interpreted by this procedure. A final solution to the problem would be the analysis of the total line shape, as in the DAVINS program;¹⁶ however, this method suffers from bad line shapes (typical of windowed spectra) and may give incorrect results.¹⁷ In the present procedure the overlapping lines, v_{calc}^{i} , were represented by their weighted averages,

$$v_{\rm wt}^{\ i} = \sum_{i}^{n} \frac{I_i^2}{\sum_{j}^{n} I_j^2} v_{\rm calc}^i \tag{1}$$

where I_i is the calculated intensity, and the rrms (wrrms) between these numbers and the observed values was minimized. Better behaviour of the couplings as a function of the acetone- d_6 to CCl₄ concentration ratio was found for 1 when this method was employed. For example, when Eqn (1) is applied in the analysis of the spectra of 1 in Table 1, the automatic assignment procedure produces, on average, a 40% lower variation of J(35), J(36), J(45) and J(46), which seem to be only weakly solvent dependent.

The spectral analyses, based on the automatic assignment procedure using Eqn (1), are summarized in Tables 1 and 2. Standard rrms and the weighted rrms values [between the numers given by Eqn (1) and the corresponding observed frequencies] are reported. As previously shown, 12,13 if the rrms of the LAOCOON type spectral analysis is not biased, the confidence limits given by the method are reliable. Usually, the confidence limits are too optimistic. For example, if a splitting is small in comparison with the resolution, a direct measurement of the splitting gives too small a value of the corresponding coupling^{15,18} and a biased rrms. The assignment of many nearly degenerate lines to one observed signal may also lead to systematic errors in couplings. Although the procedure based on Eqn (1) obviously mainly removes

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this source of systematic errors, a careful examination of the present data suggests that the real deviations are larger than given by the program. The real standard deviations can be estimated by plotting ${}^{5}J(OH, H-6)$ vs ${}^{5}J(OH, H-4)$. and ${}^{5}J(CH_{2}, H-5)$ vs. ${}^{5}J(CH_{2},H-3)$. The plots should be linear⁸ (if the couplings behave as shown in Eqn (7) and the rrms of the plot represents the real standard deviation). Plotting the values from Table 1, excluding those defined in footnote c, results in rrms values of 0.005 and 0.006 Hz (0.007 for 2), respectively. The estimate of the real standard deviation of the ${}^{5}J(CH_{2},H)$ values is about twice that calculated. Most of the difference between the observed and calculated rrms values can be accounted for by a few couplings, derived from strongly overlapping regions of the spectra and, thus, from an incomplete accounting for the overlap by Eqn (1).

Open-Clsd equilibrium and thermodynamics of the solvent dependence: EQUILA program

Qualitatively, 1 prefers the hydrogen-bonded clsd conformation, $\mathbf{1}\mathbf{A}$ in \mathbf{CCl}_4 as indicated bv ${}^{5}J(OH,H)$ and ${}^{5}J(CH_{2},H)$ values. In acetone and dioxane the intramolecular hydrogen bond is broken

Table 1. ¹H NMR spectral parameters of 2-hydroxybenzyl methyl ether (1) for various conditions^a

	Acetone-d ₆ in CCl ₄ (% v/v)									
Parameter ^b	0 (305 K)	10 (305 K)	20 (305 K)	40 (305 K)	60 (305 K)	100 (305 K)	100 (273 K)	100 (245 K)	Dioxane- <i>d</i> 8 (305 K)	CD ₂ Cl ₂ (305 K)
v(CH ₃)	340.05(2)	339.57(2)	338.65(2)	337.80(2)	337.35(2)	337.29(2)	337.22(2)	337.39(2)	332.44(2)	343.06(2)
$v(CH_2)$	460.56(2)	455.80(2)	453.40(2)	451.17(2)	450.87(2)	451.77(2)	450.20(2)	448.45(2)	446.18(2)	464.20(2)
ν(OH)	707.86(2)	733.34(2)	750.39(2)	772.85(2)	786.99(2)	805.71(2)	837.27(2)	864.41(2)	754.03(2)	740.64(2)
v(H-3)	676.80(1)	673.68(1)	673.41(1)	674.88(1)	677.24(1)	682.17(1)	684.22(1)	685.55(1)	669.20(1)	682.93(1)
v(H-4)	710.51(1)	706.96(1)	705.62(1)	705.79(1)	707.23(1)	711.02(1)	712.82(1)	714.11(1)	708.31(1)	718.42(1)
v(H-5)	671.14(1)	672.409(1)	673.19(1)	675.12(1)	677.12(1)	681.05(1)	683.23(1)	684.87(1)	678.94(1)	682.52(1)
v(H-6)	687.92(1)	699.30(1)	704.87(1)	711.53(1)	715.62(1)	721.73(1)	725.59(1)	728.37(1)	716.75(1)	701.83(1)
v(H-6) - v(H-4)	-21.11	-7.66	-0.75	5.74	8.39	10.71	12.78	14.26	8.44	-16.59
⁵ J(CH₂,H-3)	0.369(4)	0.329(4)	0.317(3)	0.314(3)	0.305(3)	0.304(3)	0.291(3)	0.282(6) ^c	0.299(3)	0.351(4)
⁶ J(CH ₂ ,H-4)	-0.479(3)	-0.491(5)	-0.494(3)	-0.505(3)	-0.500(3)	-0.500(3)	-0.508(3)	-0.534(5)	-0.485(3)	-0.501(4)
⁵ J(CH₂,H-5)	0.245(4)	0.290(4)	0.304(2)	0.319(3)	0.331(3)	0.332(3)	0.347(3)	0.358(4)	0.324(3)	0.246(5)
⁴ J(CH ₂ ,H-6)	-0.716(4)	-0.720(4)	-0.735(3)	-0.734(4)	-0.735(3)	-0.740(4)	-0.738(3)	-0.777(4)	-0.725(4)	-0.719(4)
$\Sigma^5 J$	0.614	0.619	0.621	0.633	0.636	0.634	0.638	(0.640)	0.622	0.597
⁵ J(OH,H-4)	0.467(4)	0.383(6)	0.318(4)	0.258(5)	0.239(4)	0.211(5)	0.200(6) ^c	0.173(9) ^c	0.236(5)	0.435(3)
⁵ J(OH,H-6)	0.070(6) ^c	0.176(6)	0.276(4)	0.347(5)	0.389(4)	0.424(4)	0.437(4)	0.479(6)	0.390(5)	0.085(5) ^c
$\Sigma^5 J$	(0.537)	0.559	0.594	0.605	0.628	0.635	(0.638)	(0.652)	0.626	(0.520)
J(34)	8.138(4)	8.107(4)	8.116(3)	8.104(5)	8.084(3)	8.083(3)	8.079(3)	8.080(4)	8.067(3)	8.123(4)
J(35)	1.193(4)	1.184(4)	1.177(2)	1.173(3)	1.164(3)	1.166(3)	1.162(3)	1.161(3)	1.163(3)	1.164(4)
J(36)	0.403(4)	0.398(4)	0.399(3)	0.414(5)	0.416(3)	0.403(4)	0.395(4)	0.406(4)	0.394(4)	0.412(4)
J(45)	7.398(4)	7.398(4)	7.384(3)	7.386(4)	7.383(3)	7.392(3)	7.390(4)	7.390(4)	7.382(4)	7.402(4)
J(46)	1.688(3)	1.728(5)	1.734(3)	1.728(4)	1.741(3)	1.745(3)	1.754(3)	1.768(4)	1.745(4)	1.735(4)
J(56)	7.475(4)	7.496(4)	7.509(3)	7.518(4)	7.524(3)	7.533(3)	7.528(3)	7.529(4)	7.523(4)	7.470(4)
rrms ^d	0.030	0.018	0.014	0.024	0.015	0.029	0.016	0.019	0.017	0.013
wrrms ^e	0.014	0.017	0.011	0.016	0.016	0.014	0.011	0.015	0.012	0.016

^a Chemical shifts are given with reference to TMS, and at 100 MHz.

^b Standard deviations of the parameters given in parentheses are estimated from the quality of the spectra [v(CH₃), etc.] or by the standard statistics of the program. The standard deviations for the chemical shifts were set larger than those given by the spectral analysis, to account for the uncertainties in the chemical shifts of TMS.

^c Unresolved or poorly resolved couplings. The couplings were estimated from the line broadening or from plotting, for example, ⁵J(OH,H-4) vs ⁵J(OH, H-6) and reading the unresolved couplings from this plot. The numbers obtained in this way were neglected in the D model (Table 3). The extrapolated sums of the conjugate couplings are given in parentheses.

¹ Standard rrms between every assigned signal and its corresponding calculated value.

^e 'Weighted rrms' computed as described in the text.

Table 2. ¹ H NMR spectral parameters of 2-methoxybenzyl methyl ether (2) for various conditions ^a								
	5 mol-% in CCL ^c	0.5% v/v in CCL ^d	3% v/v in CS ₂ ^e			3% v/v in CDCla	3% v/v in CDCl ₂ + HCl ^f	0.5% v/v in Ac-da
Parameter ^b	(305 K)	(305 K)	305 K	273 K	213 K	(305 K)	(305 K)	(305 K)
v(CH ₃)	376.36(2)	379.30(2)	372.40(2)	368.24(2)	363.26(2)	383.27(2)	383.09(2)	382.29(2)
$v(BzOCH_3)$	333.36(2)	334.02(2)	329.27(2)	328.77(2)	328.11(2)	341.46(2)	340.92(2)	335.23(2)
$v(CH_2)$	439.40(2)	439.01(2)	432.93(2)	432.22(2)	427.57(2)	450.39(2)	451.36(2)	443.09(2)
v(H-3)	671.69(1)	672.60(1)	666.92(1)	665.20(1)	660.15(10)	689.89(1)	687.00(1)	695.76(1)
v(H-4)	710.73(1)	711.13(1)	707.07(1)	706.67(1)	704.18(10)	725.87(1)	726.35(1)	724.51(1)
v(H-5)	684.51(1)	684.68(1)	679.16(1)	678.74(1)	676.55(10)	694.67(1)	694.64(1)	692.39(1)
v(H-6)	727.94(1)	727.39(1)	721.04(1)	720.23(1)	717.35(20)	734.22(1)	733.47(1)	733.34(1)
v(H-6) - v(H-4)	17.21	16.26	13.97	13.56	13.17	8.35	7.12	8.83
⁵ J(CH₂,H-3)	0.262(3)	0.263(2)	0.257(2)	0.248(6)	9	0.277(3)	0.287(3)	0.269(2)
⁶ J(CH ₂ ,H-4)	-0.580(3)	-0.587(2)	-0.578(2)	-0.604(6)		-0.455(4)	-0.438(3)	-0.535(1)
⁵ J(CH ₂ ,H-5)	0.377(3)	0.400(2) ^d	0.382(2)	0.379(6)		0.335(4)	0.325(3)	0.370(1)
⁴ J(CH ₂ ,H-6)	-0.844(2)	-0.846(2)	-0.835(3)	-0.849(7)		-0.697(5)	-0.678(4)	-0.782(2)
$\Sigma^5 J$	0.639	0.663	0.639	0.627		0.612	0.612	0.639
J(34)	8.219(3)	8.206(2)	8.198(2)	8.188(6)		8.240(4)	8.240(3)	8.249(2)
J(35)	1.080(3)	1.076(2)	1.068(2)	1.052(6)		1.079(3)	1.071(3)	1.067(2)
J(36)	0.372(3)	0.371(2)	0.365(2)	0.362(7)		0.367(4)	0.381(3)	0.385(2)
J(45)	7.435(3)	7.448(2)	7.427(2)	7.438(6)		7.449(4)	7.456(3)	7.445(2)
J(46)	1.787(2)	1.781(2)	1.774(2)	1.784(6)		1.788(4)	1.784(3)	1.792(2)
J(56)	7.515(3)	7.493(2)	7.464(2)	7.454(7)		7.454(5)	7.444(3)	7.475(2)
⁵ J(CH ₃ ,H-3) ^h	-0.270(10)	-0.234(30)	-0.250(40)			-0.250(40)	-0.250(40)	-0.246(30)
rrms ⁱ	0.009	0.013	0.008	0.024		0.019	0.010	0.009
wrrms ⁱ	0.009	0.008	0.007	0.021		0.012	0.009	0.005
a Objectional addition	a alizan at 100 k							

Chemical shifts given at 100 MHz.

^b Standard deviations as described in footnote b in Table 1.

^o Measured with a Varian HA-100 CW spectrometer.

^d CCl₄ containing 25% of cyclohexane-d₁₂. The H-5 signal overlaps strongly with other signals, and the value of ⁵J(CH₂,H-5) is obviously wrong.

The sample was in a capillary tube.

^f Saturated with HCI gas before degassing.

⁹ Coupling constants not analysable owing to low quality of spectra.

^h Estimated from the methoxy signal, otherwise the signal was decoupled.

^{i,j} See Table 1, footnotes d and e, respectively.

and the *open* conformation, 1B, becomes substantially populated. This paper presents an analysis based on the least-squares fitting of all the ${}^{5}J$ couplings of 1 in acetone- d_6 /CCl₄ mixtures.

In addition to the equilibrium

$$open \rightleftharpoons clsd \quad K_1, \, \Delta G_1^{\circ} \tag{2}$$

with an equilibrium constant K_1 and a free energy difference ΔG_1° , in acetone another equilibrium exists which perturbs the open/clsd ratio:

 $open + acetone \rightleftharpoons open * acetone \quad K_2, \Delta G_2^{\circ}$ (3)

In an ideal case, the expected value of a spectral parameter ^{n}J can be expressed by the molar fractions, X, and the couplings in the conformers:

$${}^{n}J = X_{clsd}{}^{n}J_{clsd} + X_{open}{}^{n}J_{open} + X_{cmplx}{}^{n}J_{cmplx}$$
(4)

where *cmplx* denotes the *open-acetone* complex.

The observed values are easily fitted with the EQUILA program,¹⁹ for which practically any type of equilibria can be simply defined. EQUILA was obtained by using a Newton-Raphson-type algorithm. The program is able, for example, to optimize simultaneously any combination of the parameters ΔH_1° , ΔS_1° , ΔH_2° , ΔS_2° , ΔH_3° , ΔS_3° and *n* used in Eqns (2), (3) and (5) and the couplings ${}^{n}J_{clsd}$, ${}^{n}J_{open}$ and ${}^{n}J_{cmplx}$ [${}^{n}J = {}^{5}J(OH, H-4)$, ${}^{5}J(OH, H-6)$, ${}^{5}I(CH, H_2)$] in the type (4) equations. ${}^{5}J(CH_{2}, H-3), \ldots$ in the type (4) equations. In other

words, the program is able to adjust simultaneously several spectral parameters [e.g. ${}^{5}J(OH,H-4)$ and $^{5}J(OH,H-6)$] which have a common thermodynamic behaviour. This procedure has some advantages over one in which each parameter is fitted separately and the resulting thermodynamic parameters are then averaged. For example, in the following analysis the constraints ${}^{5}J(OH,H-6)_{clsd} = 0$ and ${}^{5}J(OH,H-4)_{open} =$ 0 can be simultaneously applied; without the former constraint it is difficult to estimate ${}^{5}J(OH, H-4)_{clsd}$. Further, one model can be tested within one run.

The simultaneous equations for concentrations, for example, [open], [clsd], [cmplx], [acetone] and $[acetone_n]$ are solved iteratively. The iteration converges quickly if the mass law equations are logarithmically converted. The program is fast and all the present analyses were run under time-sharing operation of the VAX 11/780.

Some approximations must be considered prior to the fitting of the present data. For example, if the ^{n}J values are not measured to high accuracy at various temperatures and solvent compositions, ${}^{n}J_{open}$ and $^{n}J_{clsd}$ remain uncertain, owing to the correlations between the equilibrium constants. We can, however, assume that ${}^{5}J_{0^{\circ}}(OH,H) = 0 \text{ Hz}^{9,20}$ and that ${}^{n}J_{cmplx} =$ ^{*n*}J_{open}. The latter approximation is good for ⁵J(O \dot{H} ,H) values if the hydrogen bond to acetone has a small²⁰ (as also suggested by some INDO/FPT²¹ calculations)

Table 3. Interpretation of conformational behaviour of 1 in acetone/CCl ₄ system by using the two-site approach							
Parameter ^a (at 305 K)	A	В	с	Dpp	E	F	Gc
ΔG_1^0	-4.46(15)	-5.81(12)	-5.87(9)	-5.83(7)	-5.87	-5.87	-5.87
ΔG_2^0 or ΔH_2	0.24(15)	-2.52(19)	-1.66(10)	-6.36(14)	-3.99(10)	-1.66	-1.66
ΔG_3^{0}		5.09(34)	22.92(180)	23.88(177)		22.92	22.92
n		2.00	4.81(32)	5.03(32)	_	4.81	4.81
ΔS_2^0				-15.34(45)			
⁵ J(CH ₂ ,H-3) _{open}	0.263(7)	0.250(4)	0.248(3)	0.246(2)		—	
⁵ J(CH ₂ ,H-3) _{clsd}	0.369(6)	0.371(3)	0.370(2)	0.372(2)			
⁵ J(CH ₂ ,H-5) _{open}	0.390(7)	0.405(4)	0.407(3)	0.413(2)		—	
⁵ J(CH ₂ ,H-5) _{clsd}	0.238(6)	0.236(3)	0.236(2)	0.233(2)			
⁵ J(OH,H-4) _{clsd}	0.542(7)	0.517(4)	0.514(2)	0.515(2)			
⁵ J(OH,H-6) _{open}	0.650(10)	0.706(7)	0.716(5)	0.711(4)			
$[v(H-4) - v(H-6)]_{open}$	—				16.6(4)	37.7(9)	28.3(11)
$[v(H-4) - v(H-6)]_{clsd}$					-24.9(3)	-25.5(6)	-26.0(1)
Observations	24	24	24	29	6	6	6
rrms/ <i>r</i> ^d	0.213/0.9761	0.0108/0.9943	0.0073/0.9976	0.0071/0.9978	0.420/0.9996	1.145/0.9963	0.135/1.0000

^a The numbers in parentheses give the standard deviation in the last significant figure. If not given, the parameter was not adjusted. See also Table 1, footnote c. ${}^{5}J(OH,H-4)_{open}$ and ${}^{5}J(OH,H-6)_{clsd}$ were set to zero in all the cases. ^b The couplings at 273 and 245 K (Table 1), excluding the coulings defined in footnote c, were fitted. Using their values given in Table

1 does not change the result.

^c The polynomial fit for the solvent effect of acetone in CCl₄: $d[v(H-4) - v(H-6)] = 4.14(27)[acetone]^{1/4} - 0.24(2)[acetone].$

^d Correlation coefficient.

or no effect. ${}^{5}J(CH_{2},H)_{cmplx}$ and ${}^{5}J(CH_{2},H)_{open}$ may depend slightly on the composition of the solvent, as indicated by the solvent dependence of the couplings of 2 and explained by solvent-solute dipole interactions²² and by the flexibility of the structure. Because the solvent effect on ${}^{5}J(CH_{2},H)_{open}$ is probably approximately proportional to the effect due to the open = clsd equilibrium, the two contributions are mixed (statistically) and only perturb the reliability of ${}^{5}J(CH_{2},H)_{open}$. The approximations were applied throughout the following analysis.

If only equilibria (2) and (3) are considered, then a relatively poor fit between the observed and calculated J values is found, with an rrms of 0.021 Hz (model A, Table 3). In order to improve the fit, an equilibrium describing the decay of the activity coefficient of acetone at higher concentrations was included, namely

> *n* acetone \rightleftharpoons (acetone)_n K_3 , ΔG_3° (5)

The decay of the activity coefficient is obvious if computed and observed values are inspected for model A. When included, the equilibrium strongly improves the fit, to an rrms of 0.011 Hz if n = 2, and to an rrms of 0.0073 Hz if *n* is also optimized (models B and C). The latter by-product, an acetone cluster $(\text{Ac-}d_6)_{4.8}$ with $\Delta G_3^\circ = 22.9 \text{ kJ mol}^{-1}$, should not be taken too seriously; equilibrium (5) can merely be thought to represent the decay of the activity coefficient. The activity coefficient of acetone is expected to be higher in a non-polar medium than in neat acetone. A similar decay [with n = 4.8(4), $\Delta G_3^{\circ} = 9.4(24)$] was found in another case for acetone in cyclohexane.¹⁹ The rrms can be slightly improved by taking an equilibrium to describe the further solvation of the hydroxy group by acetone. However, these modifications have hardly any physical correspondence, and the values of the couplings and molar fractions of the sites are not changed by the modifications.

Although small, the temperature dependences of the couplings give some hints about the entropies of the reactions. The clear correlations between the changes in the ${}^{4}J$, ${}^{6}J$ and ${}^{5}J$ values suggest that these dependences are significant. The most interesting entropy differences, ΔS_1° and ΔS_2° , are stongly correlated with each other and only $\Delta S_2^{\circ} - \Delta S_1^{\circ}$ combe fixed. If $\Delta S_1^{\circ} = 0$, $\Delta S_2^{\circ} = -15 \text{ J K}^{-1} \text{ mol}^{-1}$ (model **D**). Because ΔS_1° is most probably negative, $-\Delta S_2^{\circ}$ is larger than 15 J K⁻¹ mol⁻¹. For the *tert*-butyl alcohol– acetone complex, a ΔS_2° value between -19 and -38 J K⁻¹ mol⁻¹ has been reported,²³ which implies a ΔS_1° value between -4 and -22 J K⁻¹ mol⁻¹ (corresponding to a ΔH_1° of -7.0 and -12.7, and to a ΔH_2° of -7.3 and -13.2 J mol⁻¹). Part of the temperature dependence of the couplings must account for the dynamic properties of CH₂OCH₃, as suggested by the temperature dependence of the spectral parameters of $\hat{\mathbf{2}}$. In any case, the complexation with acetone is a strongly entropically controlled reaction.

 ${}^{3}J(CH_{3},CH_{2})$ of 1 is 4.03 in benzene or 3.99 in acetone, and 4.33 Hz for benzyl methyl ether in benzene (all 35% v/v). The range is narrow and, if the values given by Dorman et al.²⁴ are used, the ratio of the *trans* and *cis* conformer populations of the CH_3 —O— CH_2 —C group is about 3/1. This implies that steric CH₃-ring interactions have no important role in the conformational behavior of the present systems.

The behaviour of the chemical shifts is of interest because both they and v(H-4) - v(H-6), for example (see Fig. 3), run parallel to the couplings (Fig. 2); these trends occur in all the solvents tried and are insensitive to the methylation of the hydroxy groups. Because the concentration dependence of v(H-5) is practically linear, it can be assumed to indicate only the solvent reaction field shift and to serve as a suitable reference signal for an extraction of the pure conformational behaviour of the other shifts (see Fig.



Figure 2. Five-bond long-range couplings of 2-hydroxybenzyl methyl ether plotted vs the acetone- d_6 concentration in CCl₄.



Figure 3. Ring proton chemical shifts of 2-hydroxybenzyl methyl ether at 100 MHz and 305 K plotted vs the acetone- d_6 concentration in CCl₄. Insert: chemical shifts as referenced to v(H-5).

3). The model E, analogous with model A, and, also, model F in which the molar fractions predicted by model C are used, yield a poor fit of v(H-4) - v(H-4) = v(H-4) - v(H-4) -6), which can be accounted for by an intrinsic solvent dependence of the chemical shifts. In model G a least-squares polynomial fit was obtained for the intrinsic effect of acetone; the model suggests the values 28 and 33 Hz for $[v(H-4) - v(H-6)]_{open}$ of 1 in CCl_4 and acetone, respectively. The estimates are very inaccurate owing to their sensitivity to the polynomial used; the ranges are about 13-28 and 26-33 Hz. However, the value for acetone was 5–13 Hz larger in every model tried. The differences for 2 in CCl_4 , acetone, CS₂ and CDCl₃ are 17.2, 8.8, 13.6 and 8.4 Hz, respectively (Table 2). The numbers do not correlate with ${}^{n}J(CH_{2},H)$ in a simple manner, and obviously inlude both structural and medium contributions. The difference for $\mathbf{1}_{clsd}$ is about $-25 \, \text{Hz}$,

indicating that the most important contribution comes from the conformation of the hydroxy group. According to the dynamic model,²⁵ a larger difference implies a stronger planarity of the CH_2 —O bond.

The Open and Clsd conformers

The structures of both conformers can now be estimated. If the phenol hydroxy group remains (the two-fold rotation barrier of phenol is 14 kJ mol^{-1} in the gas phase²⁶) in the aromatic ring plane, then only that of the CH₂-ring rotation needs to be considered. $^{n}J(CH_{2},H)$ values for 1, as estimated by the model C thermodynamics and the values for 2, can now be summarized:

	1_{open}	1_{clsd}	Z _{open} in acetone	2_{open} in CCl ₄
${}^{5}J(CH_{2},H-3)$	0.248	0.370	0.269	0.262
$J(CH_2, H-4)$	-0.522	-0.477	-0.535	-0.580
$^{5}J(CH_{2},H-5)$	0.407	0.236	0.370	0.377
$J(CH_2H-6)$	-0.759	-0.711	-0.782	-0.844

The following discussion assumes that ${}^{6}J(\theta)$ and ${}^{5}J(\theta)$ are given by

$${}^{6}J(CH,H) = {}^{6}J_{\pi}{}^{0}\sin^{2}\theta \tag{6}$$

$${}^{5}J(CH,H) = {}^{5}J_{\pi}{}^{0}\sin^{2}\theta + {}^{5}J_{\sigma}{}^{0}\sin^{2}(\theta/2)$$
(7)

with ${}^{6}J_{\pi}{}^{0} = -1.018$, ${}^{5}J_{\pi}{}^{0} = 0.196$ and ${}^{5}J_{\sigma}{}^{0} = 0.434$ Hz, the values suggested by a dynamic approach.²⁵

Because the rotation barrier in benzyl alcohol itself is low, the internal rotation in the 2-hydroxy and 2-methoxy derivatives is controlled mainly by interactions with the 2-substituent. The freedom of the tilting about the aromatic plane is represented by ${}^{6}J(CH_{2},H)$. According to the parameterization suggested the range of ${}^{6}J$ extends from -0.275 ($\phi = 90^{\circ}$) to -0.825 Hz ($\phi = 180^{\circ}$). A fully free tilting, from a ϕ of 0° to 90°, would result in ${}^{6}J = -0.549$ Hz, a value



near to the values predicted for ${}^{6}J_{open}$. The non-equivalence of the ${}^{5}J(CH_2,H)$ values shows that $\phi > 90^{\circ}$ is favoured. One might expect that the energetics of $\mathbf{1}_{open}$ and $\mathbf{2}_{open}$ should be very similar; this is not true for the *open* conformer couplings in acetone. This can be partly explained by the statistical uncertainty of the extrapolated values for $\mathbf{1}_{open}$ and, partly, by slightly different energetics of the systems, revealed by simple molecular mechanics.²⁵ If ${}^{5}J_{\pi}^{0}$ is substantial, the sum of the ${}^{5}J(CH_2,H)$ values should correlate with ${}^{6}J(CH_2,H)$, as occurs in most of the data. The extrapolated values of $\mathbf{1}_{open}$ are an exception, and must be explained by the solvent dependence of the $\mathbf{1}_{open}$ values. The thermodynamics described for the acetone solutions are mostly determined by the ${}^{5}J(OH,H)$ data used in the EQUILA fitting, and similar results are obtained if the ${}^{5}J(CH_{2},H)$ values are not used in the EQUILA analysis.

The values of ${}^{n}J_{clsd}$ of 1 are more accurate, being extrapolated over a narrow concentration range. If the clsd conformer is taken as rigid, the CH₂OCH₃ being anchored by a hydrogen bond, a straightforward solution for ϕ from Eqns (6) and (7) gives $\phi = 131.4^{\circ}$ $(130.3^{\circ} - 132.5^{\circ})$ if a 0.01 Hz uncertainty in the observation is assumed), 128.3° ($124.9^{\circ} - 131.2^{\circ}$) and 123.6° (116.8° – 131.1°) by using ${}^{6}J(CH_{2}, H-4)$, ${}^{5}J(CH_{2}, H-3)$ or ${}^{5}J(CH_{2}, H-5)$, respectively. ${}^{6}J$ gives the most reliable value because its behaviour around 120° is nearly linear and a small tilting around the equilibrium angle is, therefore, averaged. If the model N parameters²⁵ are used, then values of $\phi = 125.1^{\circ}$ $(124.0^{\circ} - 126.1^{\circ})$, 123.5° $(115.9^{\circ} - 133.4^{\circ})$ and 118.3° $(114.7^{\circ} - 121.9^{\circ})$ are obtained. The numbers show that the ${}^{6}J$ couplings give the best estimate of the angle, and that the largest uncertainty in the numbers comes from the uncertainty of the coupling behaviour, not from the inaccuracies in the data or the approximations used.

CONCLUSION

The intramolecular hydrogen bond in 2-hydroxybenzyl methyl ether is rather strong but entropically

unfavorable, as discussed in the following paper,²⁵ and is opened by solvents able to form a specific hydrogen bond with the hydroxy group. The dielectric constant of the solvent is not important: the intramolecular hydrogen bond is broken by both dioxane and acetone. As a result, the conformations of the hydroxy and benzyl fragments are strongly correlated and can be controlled by hydrogen-bonding solvents. The torsion angle O—CH₂—C-1—C-6 (ϕ) of the *clsd* conformation, as estimated from ⁶J(CH₂,H) is *ca* 130°. The ${}^{5}J(CH_{2},H)$ couplings appear to be more difficult to apply for the estimation of the angle, owing to the more complex properties of the coupling. Some chemical shifts are clearly diagnostic and qualitatively useful in cases where the couplings cannot be resolved or where they are unobservable owing to exchange processes. The ring proton chemical shifts appear to be sensitive to the conformation of the hydroxy group; unfortunately, the behaviour cannot be extracted accurately from the present data.

This study suggests that even rather small variations in the long-range couplings can be used in conformational studies.

Acknowledgements

I thank Professor Ted Schaefer for his challenging criticisms and for his encouragement. I thank the Academy of Finland and the Natural Sciences and Engineering Research Council of Canada (grant A1296) for financial support.

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