Nuclear Magnetic Resonance and Molecular Orbital Study of Internal Hydrogen Bonding in Salicyl Alcohol. Principal Site Analysis based on the Sidechain Methylene and Hydroxy Proton Long-range Coupling Constants

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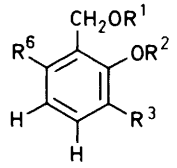
The ^1H n.m.r. spectra of 2-hydroxybenzyl, 2-methoxybenzyl, 2-hydroxy-3-methoxy-, and 2,6-dimethoxy-benzyl alcohols are studied in various solvents. The long-range proton–proton spin–spin coupling constants, certain chemical shifts, and some STO-3G MO calculations are used to characterize the conformational behaviour of salicyl alcohol. The observed variation of the coupling constants is reproduced by a three-site model: salicyl alcohol and its 2-methoxy derivative seem to have three principal conformations: *clsd1* (= closed 1) with a hydrogen bond between the phenolic hydrogen and CH_2OH, *open* with a rather freely rotating CH_2OH sidechain, and *clsd2* with a hydrogen bond between the CH_2OH hydroxy group and the phenolic oxygen atom. The free energy of the internal hydrogen bond in *clsd2* is smaller than in *clsd1*. The presence of the *clsd2* form is inferred by indirect methods, not from direct indicators like hydroxy stretching frequencies or proton chemical shifts. The hydrogen-bonded forms predominate in non-polar solvents. The hydrogen bonds are opened by nucleophilic solvents. For D_2O solutions a deuterium-bridged structure is suggested.

The conformational behaviour of salicyl alcohol (**1**) in solution is poorly known, because of a lack of convenient conformational probes. The available knowledge is based mostly on stretching frequencies and proton chemical shifts of the hydroxy groups.[1–3] In previous work,[4,5] models for the conformational behaviour of the CH_2 and hydroxy long-range coupling constants in 2-hydroxy- (**2**) and 2-methoxy-benzyl methyl ethers (**3**) were derived. These compounds were shown to have two principal conformations, one with an intramolecular hydrogen bond between the sidechains, the other without the hydrogen bond. The former was assumed to be relatively rigid, while in the latter the CH_2OCH_3 moiety tilts rather freely about the ring plane. The equilibrium between the conformers named *clsd* and *open* was sensitive to solvent. The opening of the hydrogen bond in (**2**) inverts the conformations of the sidechains.[4,5] The present paper concerns compounds (**1**) and (**4**)—(**6**).

In salicyl alcohol there are three possible intramolecular hydrogen bonds. The hydrogen bond between the phenolic hydrogen atom and CH_2OH is indicated by hydroxy stretching frequencies and ^1H n.m.r. chemical shifts and, being similar to that of (**2**), it is probably relatively strong. The two others, the hydrogen bond of the CH_2OH group to the phenolic oxygen atom, and the interaction between the CH_2OH hydroxy group and the ring π-system, are supposed to be weak.[1,6] The observed CH_2OH stretching frequencies (3 610 and 3 635 cm^{-1})[1] and hydroxy proton chemical shift (δ 1.8)[3] of 2-methoxybenzyl alcohol (**4**), do not differ greatly from those of benzyl alcohol (3 635, 3 615 cm^{-1} and δ 1.1),[1,3] implying that the interaction would also be weak in (**1**). There is little evidence for an OH • • • π-interaction; the stretching frequencies of the hydroxy group in benzyl alcohol can be interpreted without such an interaction.[7] Also the OH chemical shift of benzyl alcohol indicates no remarkable interaction.[3] The rotation of CH_2OH with respect to the ring is assumed to be rather free (n.m.r.,[8] STO-3G *ab initio*[3]) with a minimum-energy conformer in which CO lies in the ring plane, or it is suggested (by electron diffraction in the gas phase) that the CO-ring dihedral angle (ψ_1) is *ca.* 60°[9] with a barrier of *ca.* 4 kJ mol at ψ_1 0°.[10] Isoelectronic benzyl fluoride is shown to exist in a similar conformation but with a barrier of 1—2 kJ mol^{-1} only.[10,11] The electron diffraction results are rather inaccurate in this case. The ψ_1 value of *ca.* 60° can be explained simply by steric interactions.[10] The energy difference between benzyl fluoride and benzyl alcohol indicates a weak OH • • • π interaction. An indication is the $^3J(CH_2,OH)$ coupling[3] (*ca.* 6 Hz), which shows that the OH points to the ring more than expected on the basis of primary alcohols (*ca.* 5 Hz[12]). It has been, however, claimed that the interaction is not hydrogen bond in the same sense as found, for example, for but-3-en-1-ol[13] and *syn*-norborn-2-en-7-ol[14] in which the bonds can be seen from i.r. frequencies (*ca.* 3 575 cm^{-1}). The conformation of the hydroxy group in benzyl alcohol is thought to be partly a consequence of repulsion between oxygen lone-pair and π-electrons.[15–17] A similar dilemma exists for cyclopropylmethanol.[18]



	R^1	R^2	R^3	R^6
(**1**)	H	H	H	H
(**2**)	CH_3	H	H	H
(**3**)	CH_3	CH_3	H	H
(**4**)	H	CH_3	H	H
(**5**)	H	H	OCH_3	H
(**6**)	H	CH_3	H	OCH_3

If the CR_2OH oxygen atom is forced into the ring plane, there appears a clear hydrogen bond to the methoxy group in the *ortho* position.[19] The absence of the hydrogen bond in (**4**) is odd if the rotation of CH_2OH is assumed to be free or to have a

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Table 1. Some STO-3G level *ab initio* calculations for salicyl alcohol (**1**)

Conformer	Energy (kJ mol^{-1})[a]	Dipole moment[b]	Optimized structural parameters[c]								
			ψ_1	ψ_2	ψ_3	*A*1	*A*2	*A*3	*A*4	*A*5	*R*1	*R*2
clsd1	0.00	2.45	146.9	−71.0	13.1	119.8	111.4	104.2	122.5	104.4	0.9886	0.9925
	0.17	3.04	147.3	169.7	16.0	120.6	108.9	105.4	122.8	104.2	0.9879	0.9914
	3.97	3.24	165.1	180*	0*	122.7	110.1	105.9	124.0	105.1	0.9868	0.9894
	4.20	3.28	180*	180*	0*	123.3	110.5	106.3	124.2	105.2	0.9862	0.9893
clsd2	7.75	2.72	126.3	58.0	180*	118.5	112.7	102.6	116.8	106.1	0.9895	0.9870
	14.23	2.57	90*	62.8	180*	119.4	112.4	103.2	117.3	105.4	0.9906	0.9880
	30.01	1.01	96.4	60*	−15.9	121.5	112.4	103.8	124.4	106.4	0.9911	0.9871
open	15.79	1.44	0*	180*	180*	118.6	109.3	103.7	117.1	105.3	0.9906	0.9883
	37.58	0.94	180*	180*	180*	123.7	112.3	103.1	119.3	104.6	0.9922	0.9896

[a] The total energy −414.147 80 a.u.. [b] In Debyes. [c] The dihedral angles ψ_1—ψ_3 are defined in the text. *A*1 = angle (in degrees) H_3C–O–CH_2, *A*2 = O–CH_2–C(1), *A*3 = CH_2–C(1)–C(2), *A*4 = C(1)–C(2)–OH, *R*1 = distance (in Å) H–OCH_2, *R*2 = H–OC(2). Also the bond lengths and angles of the CH_2 group were optimized while treating its C–H bonds as equivalent. * These parameters were not optimized.

minimum at ψ_1 60° and 120° and if there is no competitive interaction between OH and the ring. Because the OH-proton–ring distance is large, leading to poor overlap, the contact angle with the π-cloud is *ca.* 0°, and because the electric fields of the π-system and *ortho*-methoxy are at an angle of *ca.* 90°, it is possible that the i.r. and chemical shifts probes do not tell the whole truth about the interaction. Interpretation of chemical shift information is disturbed by the other conformers and by the magnetic anisotropy of the ring.

In this study we apply the coupling behaviour determined in our previous study.[4,5] It was hoped to elicit information about the structure and behaviour of salicyl alcohol in solution and about the intramolecular hydrogen bonds from details of the conformation of the CH_2OH system. We also report some STO-3G level *ab initio* calculations for salicyl alcohol and discuss the so-called 'principal site analysis.'[20]

Experimental

Materials.—Compounds (**1**) and (**5**) were from Aldrich and were purified by sublimation at low pressure. The benzyl methyl ethers were prepared by the NaH–CH_3I method.[4] Benzyl alcohol and (**6**) were from Aldrich and were distilled before preparing the n.m.r. samples.

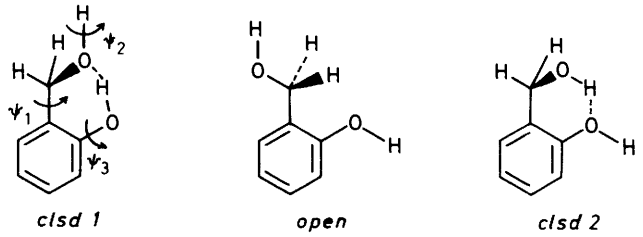
Spectra.—The samples were dried as previously described,[21] using molecular sieve 4 Å pellets. [$^2H_6$]Acetone solutions were filtered in a dry box before degassing by the freeze–pump–thaw technique. In samples of (**1**) and (**5**) intermolecular exchange of the phenolic protons was difficult to stop and only succeeded for (**1**) at lowered temperatures and at very low concentrations. The exchange of the CH_2OH proton was difficult to stop in CCl_4 and for (**4**) it was stopped after a few days, and began again a few days later. The exchange of the benzyl hydroxy protons was easily stopped in [$^2H_6$]acetone. Compounds (**1**) and (**5**) are poorly soluble in CCl_4 and saturated solutions of <0.1% (w/v) were used, leading to spectra of a relatively low quality.

The spectra were analysed in the way discussed before.[4]

Results and Discussion

Three-site Model.—Initially, *ab initio* calculations were used to characterize the structures of the conformers. This approach yields rather reasonable energetics (in the light of n.m.r. data) for 2-fluorobenzyl alcohol.[22] A comparison of the $^nJ(CH_2,H)$ couplings with the present data indicates that the conformational behaviour of the 2-fluorobenzyl alcohol is similar to that of (**4**).

STO-3G MO calculations (Table 1) suggest three principal



conformations for salicyl alcohol excluding the conformations of the benzyl hydroxy, namely *clsd1*, *clsd2*, and *open*. According to the calculations, ψ_1 at the minimum energy (147°) in *clsd1* is close to that in (**2**) (148°).[5] The energy for ψ_1 180° (4 kJ mol^{-1}) is clearly lower than that of (**1**) (14 kJ mol^{-1}). The calculations also suggest that the benzyl hydroxy proton may have two conformations with energy difference of only 4 kJ mol^{-1}, *exo* and *endo*, with ψ_2 *ca.* 180 and 60°. The calculations indicate that *clsd2* lies 7.75 kJ mol^{-1} above *clsd1* and if the latter is assumed to be doubly degenerate, the total free energy difference at 305 K is as high as 9.50 kJ mol^{-1}. The spectroscopic results below suggest that the energy difference of the *clsd1* and *clsd2* forms is clearly smaller in solution.

In order to obtain numerical values of the populations and energetics of the system, the following 'principal site approach'[20] was applied for the present data. For each coupling, ^nJ, in each compound, we have equations (1). Because

$$^nJ_{obs} = X_{clsd1}{}^nJ_{clsd1} + X_{clsd2}{}^nJ_{clsd2} + X_{open}{}^nJ_{open} \quad (1)$$

there are up to six observed couplings for each compound which are different for each conformer, the molar fractions *X* of the forms can be extracted from the corresponding six simultaneous equations, if the values of ^nJ_i are known. Because the sum of the molar fractions is 1, there are four degrees of freedom available to solve for unknown ^nJ_i values. If the equilibrium is maintained by solvent or substitution so that the structures and the couplings of the forms remain unchanged, each new condition contributes four new degrees of freedom available for finding ^nJ_i values. For example, we assume that the *open* forms of (**1**) and (**4**) are similar. In the following analysis we also assume that the *open* and *clsd2* conformers of (**1**) and (**4**) are identical and independent of solvent and temperature. This strategy was tested in a study of substituted methylenemalonaldehydes.[20] By using five couplings [$^nJ(CH_2,H)$ and ^2J(OH,4-H)] for seven conditions given in Tables 2 and 3 (excluding the D_2O solutions) one obtains 35 simultaneous equations with 29 unknowns. To improve the statistics, $^5J(OH,4\text{-}H)_{clsd1}$ is set at

Table 2. Aromatic proton chemical shifts (in Hz[a]) and coupling constants for salicyl alcohol (**1**)

Parameter[b]	0.1 w/v % $CCl_4 + C_6D_{12}$[c] at 305 K	0.5 w/v % CD_2Cl_2 at 305 K	0.5 w/v % $[^2H_6]$Acetone at 305 K	at 253 K	at 233 K	0.5 w/v % $D_2O + [^2H_6]Me_2CO$[d] at 305 K	0.5 w/v % D_2O at 305 K
ν_3	677.82(1)	684.59(1)	679.67(1)	681.50(1)	682.31(5)	689.12(1)	692.13(1)
ν_4	710.11(5)	718.68(1)	708.57(1)	710.41(1)	711.10(5)	720.96(1)	725.38(1)
ν_5	671.28(1)	683.91(1)	679.75(1)	683.32(1)	684.87(5)	693.39(1)	696.80(1)
ν_6	689.06(1)	704.37(1)	722.10(1)	731.13(1)	734.79(5)	730.68(1)	731.71(1)
$\nu_6 - \nu_4$	−21.05	−14.31	13.53	20.72	23.69	9.72	6.33
$^5J(CH_2,3\text{-H})$	0.361(4)	0.352(4)	0.307(2)[h]	0.254(5)		0.316(4)	0.330(4)
$^6J(CH_2,4\text{-H})$	−0.456(20)[e]	−0.456(4)	−0.537(2)[h]	−0.571(5)		−0.420(3)	−0.385(4)
$^5J(CH_2,5\text{-H})$	0.260(4)	0.267(3)	0.334(1)[h]	0.349(5)		0.314(4)	0.285(4)
$^4J(CH_2,6\text{-H})$	−0.701(4)	−0.703(4)	−0.766(7)[h]	−0.807(5)		−0.644(3)	−0.590(4)
$^5J(OH,4\text{-H})$	0.360(30)[e,g]	0.363(5)	0.190(20)[f]	0.168(6)			
$^5J(OH,6\text{-H})$	0.210(20)[e,f]	0.207(20)[g]	0.400(30)[g]	0.433(7)			
$\Sigma\,^5J$	0.570	0.570	0.590	0.601			
J_{34}	8.122(5)	8.121(4)	8.063(2)[h]	8.032(5)		8.103(4)	8.107(4)
J_{35}	1.183(4)	1.169(4)	1.162(2)[h]	1.152(5)		1.157(4)	1.146(4)
J_{36}	0.390(4)	0.414(4)	0.395(2)[h]	0.388(5)		0.404(4)	0.405(5)
J_{45}	7.426(6)	7.412(4)	7.383(2)[h]	7.390(5)		7.423(4)	7.446(4)
J_{46}	1.729(6)	1.710(4)	1.748(4)[h]	1.760(5)		1.754(3)	1.751(4)
J_{56}	7.493(4)	7.501(4)	7.521(2)[h]	7.524(5)		7.537(4)	7.530(5)
R.r.m.s.	0.031	0.044	0.010	0.028		0.016	0.020
W.r.r.m.s.[i]	0.018	0.017	0.007	0.022		0.011	0.011

[a] The chemical shifts at 100 MHz. [b] The numbers in the parentheses are the standard deviations given by standard statistics or limits within which the real couplings are most probable, if the signals are broadened and coupling estimated as described in footnotes *e*—*g*. [c] About 25 v/v % of $[^2H_{12}]$cyclohexane used as lock. [d] About 25% v/v of $[^2H_6]$acetone. [e] Signals broadened, the value is obtained by assuming the coupling equal to that in CD_2Cl_2; the other couplings and the couplings for (**2**)[4] suggest that the conformations and the *clsd1*:*open* ratios are similar in these two solvents. [f] Signals broadened, the coupling was estimated from the linewidths or if the splittings small in comparison with linewidth, the real differences of lines were estimated by using correction factors calculated for doublets. [g] Signals broadened, the value estimated by the principle described in ref. 4 (Table 1). [h] The couplings were determined from a chemically OH-decoupled spectrum. [i] Weighted r.r.m.s.[4]

Table 3. Aromatic proton chemical shifts (in Hz[a]) and coupling constants for 2-methoxybenzyl alcohol (**4**)

Parameter[b]	5 mol %[d] CCl_4 at 305 K	0.5 v/v % $CCl_4 + C_6D_{12}$[c] at 305 K	0.5 v/v % $[^2H_6]Me_2CO$ at 305 K
ν_3	674.72(1)	675.99(1)	692.02(1)
ν_4	713.33(1)	714.06(1)	720.50(1)
ν_5	684.08(1)	684.78(1)	691.38(1)
ν_6	720.73(1)	720.98(1)	740.86(1)
$\nu_6 - \nu_4$	7.40	6.92	20.36
$^5J(CH_2,3\text{-H})$	0.302(4)	0.304(6)	0.248(3)
$^6J(CH_2,4\text{-H})$	−0.460(4)	−0.433(6)	−0.595(2)
$^5J(CH_2,5\text{-H})$	0.324(1)	0.309(5)	0.399(2)
$^4J(CH_2,6\text{-H})$	−0.701(1)	−0.665(7)	−0.872(2)
$^3J(OCH_3,3\text{-H})$	0.285(10)		0.268(20)
J_{34}	8.213(4)	8.215(6)	8.214(2)
J_{35}	1.051(4)	1.046(5)	1.061(2)
J_{36}	0.366(4)	0.353(6)	0.369(2)
J_{45}	7.470(4)	7.492(2)	7.453(2)
J_{46}	1.767(4)	1.765(6)	1.784(2)
J_{36}	7.404(4)	7.399(6)	7.457(2)
R.r.m.s	0.016	0.022	0.011
W.r.r.m.s.[i]	0.014	0.019	0.006

[a–c,i] As Table 2. [d] The real concentration was clearly smaller due to adsorption on molecular sieve 4 Å used for drying the sample

0.514 Hz (as derived in ref. 4); $^5J(OH,6\text{-H})_{clsd2} = {}^5J(OH,4\text{-H})_{open} = 0.000$ Hz. The results are not sensitive to these assumptions. A change of 0.010 Hz in $^5J(OH,4\text{-H})_{clsd1}$ changes the refined spectral parameters by *ca.* 0.002 Hz and the molar fractions by 0.01. For (**4**) we set $X_{clsd1} = 0$, in practice by setting $^5J(OH,4\text{-H})$ to 0 and weighting the corresponding equations by a factor of 10. Due to uncertainties in $^5J(OH,H)$, only $^5J(OH,4\text{-H})$ was included in the analysis. It would also be reasonable to assume that the parameters of *clsd1* are equal with those of (**2**). This did not, however, essentially change the result and the statistics. The value of $^5J(CH_2,3\text{-H})$ of (**1**) in acetone at 253 K appeared to be most probably biased and was rejected in the final calculation where we optimized 12 spectral parameters and 14 molar fractions, given in Table 4, on the basis of 34 observations. The calculations were performed with the program MUSITE.[20] The advantages of the present strategy over other procedures are that all the available data are fitted simultaneously and that any constraints can be easily imposed and tested. The 'principal site' analysis described above gives the best overall statistical picture from the present data: the reliability of the result must be considered on the grounds of information not included in the fitting.

The results of the three-site analysis are given in Table 4. The total r.r.m.s. (= residual root mean square) was *ca.* 0.010 Hz, which is reasonable in the light of the accuracies of the couplings (the standard deviations given by the spectral analysis were 0.002—0.007 Hz) and the approximations made.

In previous papers[4,5] it was shown that $^6J(CH_2,H)$ is a reliable measure of ψ_1 if the conformer is rigid. If this is also assumed for *clsd2*, then the value −0.344 Hz corresponds now to ψ_1 116(3)°, maybe to 120(3)°, if the dynamic approach[5] is used. For ^6J we used $^6J = -1.0 \sin^2\theta$ (with θ = CH–ring dihedral angle) for one proton, expanding the formula for a tetrahedral CH_2 group. The standard deviations given in the parentheses are based on the standard deviation of 0.020 Hz in $^6J(CH_2,H)$ including the r.r.m.s. and the uncertainty of the model for ^6J. The STO-3G value of ψ_2 of *clsd2* is 126.3°. This, among some other trends, suggests that the three-site model and the populations given by the approach are essentially correct.

The energy difference of the *clsd1* and *clsd2* forms is worth a discussion. If the free energy difference derived above from the STO-3G calculations were correct, then the population of the

Table 4. Three-site analysis for salicyl alcohol and 2-methoxybenzyl alcohol

	Optimized parameters[a]			Fit[b]
	clsd1	*clsd2*	*open*	(Hz)
$^5J(CH_2,3\text{-}H)$	0.377(10)	0.377(14)	0.246(10)	0.010
$^6J(CH_2,4\text{-}H)$	−0.470(11)	−0.344(10)	−0.615(13)	0.010
$^5J(CH_2,5\text{-}H)$	0.247(10)	0.263(15)	0.405(14)	0.010
$^4J(CH_2,6\text{-}H)$	−0.715(10)	−0.560(10)	0.873(15)	0.010
$^5J(CH_2,4\text{-}H)$	0.514	0.000	0.000	
X_i, (**1**) in CCl_4	0.70(0.0)	0.22(2.9)	0.08(5.5)	0.007
X_i, (**1**) in CD_2Cl_2	0.71(0.0)	0.19(3.3)	0.10(5.0)	0.006
X_i, (**1**) in $[^2H_6]$-Me_2CO, 305 K	0.37(0.8)	0.12(3.6)	0.51(0.0)	0.008
X_i, (**1**) in $[^2H_6]$-Me_2CO, 253 K	0.33(1.5)	0.02(7.1)	0.65(0.0)	0.012
X_i, (**4**) in CCl_4		0.56(0.0)	0.44(0.6)	0.003
X_i, (**4**) in CCl_4 + C_6D_{12}		0.68(0.0)	0.32(1.9)	0.005
X_i, (**4**) in $[^2H_6]$-Me_2CO		0.03(8.6)	0.97(0.0)	0.008

[a] The numbers in parentheses give the standard deviations of the optimized parameters (for spectral parameters) and the relative energies (in kJ mol^{-1}) corresponding to the populations for the molar fractions X_i. If not given, the spectral parameter was not optimized. The standard deviations of the molar fractions were <0.04. The standard deviations of the energies are strongly dependent on the value of the energy: typical standard deviations for energies of 1—10 kJ mol^{-1} were 0.5—1.5 kJ mol^{-1}. The standard deviations were computed by a procedure in which random errors were induced into the best calculated values. [b] The fit represents how well each parameter is predicted by the model or how good the fit is for each compound. The expression and meaning are given in ref. 20.

clsd2 form at 300 K would be essentially zero. A two-site model leads to a good fit for the data for (**1**). However, the structures of the resulting *clsd1* and *open* forms (with $^6J_{clsd1}$ −0.367 and $^6J_{open}$ −0.655 Hz) are very much different from those of $(\mathbf{2})_{clsd}$ (−0.470)[4] and (**4**) (−0.595) observed directly in acetone. Because this seems improbable we believe that the three-site model is better. Furthermore, ^5J(OH,4-H) of 0.363 Hz in (**1**) in CCl_4 is smaller than that of (**2**) (0.467 Hz), which indicates that the population of *clsd1* is smaller for (**1**) in CCl_4 than that for (**2**), probably due to the *clsd2* form. The whole picture of *clsd2* remains incomplete without i.r. and hydroxy proton chemical shift information; these are discussed later.

At this point the conformational results can be summarized. First, the *clsd2* form seems more stable than given by the STO-3G method. Second, the *clsd2* form is effectively opened by acetone solvation, in comparison with the *clsd1* form.[4] This is directly seen from the couplings of (**4**) in Table 3. Third, the *open* form is more planar than that of (**2**), as shown by the value of ^6J of (**4**) in acetone (−0.595 Hz) and $^6J_{open}$ of (**1**) (−0.600 by the three-site analysis) in comparison with $^6J_{open}$ of (**2**) (−0.520 Hz[4]). These values suggest that ψ_1 for the minimum energy of the *open* form is near to zero. The temperature dependence of the populations of (**1**) in acetone suggests that *open* in acetone is not entropically favoured over the other conformers: this result may well be accounted for by the hydrogen-bonding entropy of the acetone complexes,[23] which may also account for the temperature dependence of the spectral parameters of *open*, which is likely to be more planar at low temperatures.[5]

The same model can be applied to 2-fluorobenzyl alcohol.[22] We simply state that the energetics of this system is practically identical with that of (**4**). There is one spectral analytical point to comment on here: the ^5J couplings given for 2-fluorobenzyl alcohol are smaller than those of (**4**) but the ratios of the values are equal. This is accounted for by a lower resolution in the spectra of 2-fluorobenzyl alcohol, as discussed in ref. 4.

Table 5. Aromatic proton chemical shifts (in Hz[a]) and coupling constants for 2-hydroxy-3-methoxybenzyl alcohol (**5**)

Parameter[b]	0.2 v/v % CCl_4 + C_6D_{12}[c] at 305 K	0.5 v/v % C_6D_6 at 305 K	0.5 v/v % $[^2H_6]Me_2CO$ at 305 K
ν_4	669.66(10)	641.07(1)	684.96(1)
ν_5	671.14(20)	670.07(1)	676.73(1)
ν_6	680.20(20)	687.83(1)	695.00(1)
$^6J(CH_2,4\text{-}H)$	*d*	−0.410(5)	*d*
$^5J(CH_2,5\text{-}H)$		0.296(5)	
$^4J(CH_2,6\text{-}H)$		−0.663(12)	
^5J(OH,4-H)	small	small	small
^5J(OH,6-H)	0.505(20)	0.491(11)	0.557(10)
$^5J(OCH_3,4\text{-}H)$		0.240(50)	
J_{45}		8.096(7)	
J_{46}		1.427(8)	
J_{56}		7.743(11)	
R.r.r.m.s		0.015	0.015

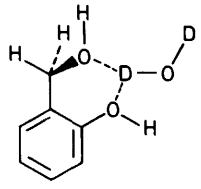
[a–c] As Table 2. [d] Aromatic region strongly second-order type. The compound poorly soluble in the system and probably adsorbed by molecular sieve used in drying the sample.

Table 6. Aromatic proton chemical shifts (in Hz[a]) and coupling constants for 2,6-dimethoxybenzyl alcohol (**6**)

Parameter[b]	0.5 v/v % in CCl_4 + C_6D_{12}[c] at 305 K	5 v/v % in $[^2H_6]Me_2CO$ at 305 K
ν_3	645.05(1)	662.79(1)
ν_4	707.34(1)	720.42(1)
$^5J(CH_2,3\text{-}H)$	0.349(5)	0.331(9)
$^6J(CH_2,4\text{-}H)$	−0.294(4)	−0.259(7)
$^5J(OCH_3,3\text{-}H)$	0.200(50)	0.200(50)
J_{34}	8.344(3)	8.361(7)
R.r.m.s.	0.010	0.010

[a–c] As Table 2.

Salicyl Alcohol in D_2O.—The couplings of (**1**) in D_2O are odd. If the three-site model is applied to (**1**) in D_2O, using the spectral parameters given by the previous analysis, one obtains X_{clsd1} = 0.01, X_{clsd2} = 0.87, and X_{open} = 0.12 with r.r.m.s. 0.007 Hz. The corresponding values for acetone–D_2O solution (25:75) are 0.01, 0.71, and 0.28. An explanation for the behaviour of (**1**) in D_2O is that D_2O forms a deuterium bridge between the two oxygen atoms of (**1**). Rather similar behaviour is observed for 2-methoxybenzyl methyl ether (**3**) in $CDCl_3$,[5] and for some methylenemalonaldehydes.[24] Because the structure in D_2O is similar to the *clsd2* conformer, X_{clsd2} now represents the sum (X_{clsd2} + X_{D_2O}), in which the latter term probably predominates.



The chemical shifts of the aromatic ring protons, excluding 5-H, are sensitive to the conformations of the sidechains.[4] The three-site approach was tried for the chemical shifts, but it appeared that the chemical shifts were sensitive to solvent and

Table 7. Proton chemical shifts[a] and coupling constants of the sidechains of some benzyl and salicyl alcohol derivatives

Compound	v or w/v %	Solvent[b]	T/K	$^3J(CH_2OH)$[d]	$\nu(CH_2)$	$\nu(CH_2OR)$	$\nu(PhOH)$	$\nu(PhOCH_3)$
1-CH_2OH	0.1	$CCl_4 + C_6D_{12}$	305	6.129(15)	458.30	113.12		
	0.5	$[^2H_6]Me_2CO$	305	5.804(20)	462.23	407.48		
1-CH_2OH, 2-OCH_3	0.1	$CCl_4 + C_6D_{12}$	305	6.607(20)	455.39	161.22		384.24
	0.5	$CCl_4 + C_6D_{12}$	305		455.38	167.10		384.40
	5.0	CCl_4	305[e]	6.490(50)	453.00	197.63		380.64
	0.5	$[^2H_6]Me_2CO$	305	5.901(20)	463.11	382.08		
1-CH_2OH, 2,6-$(OCH_3)_2$	0.1	$CCl_4 + C_6D_{12}$	305	7.022(10)	459.18	182.96		382.51
	0.5	$[^2H_6]Me_2CO$	305	6.354(20)	464.29	317.36		
1-CH_2OH, 2-OH	0.1	$CCl_4 + C_6D_{12}$	305	5.930(100)	478.63	182.65	697.83	
	0.1	CD_2Cl_2	305	5.585(20)	485.42	222.72	723.71	
	0.5	$[^2H_6]Me_2CO$	305	5.498(10)	474.39	434.03	831.59	
	0.5	$[^2H_6]Me_2CO$	253	5.589(10)	472.75	460.30	866.92	
	0.5	$[^2H_6]Me_2CO$	233	*e*	471.0[e]	471.0[e]	880.48	
1-CH_2OH, 2-OH, 3-OCH_3	0.1	$CCl_4 + C_6D_{12}$	305	6.100(100)	459.72	180.31	570.97	386.95
	0.1	CD_2Cl_2	305	6.322(50)	469.07	212.78	602.02	338.12
	0.5	C_6H_6	305	6.170(50)	469.10	164.47	569.98	315.98
	0.5	$[^2H_6]Me_2CO$	305	5.845(20)	468.59	391.58	748.67	383.13
1-CH_2OCH_3	0.5	$CCl_4 + C_6D_{12}$	305		437.44	328.81		
	0.5	$[^2H_6]Me_2CO$	305		442.20	332.19		
1-CH_2OCH_3, 2-OH	0.5	$CCl_4 + C_6D_{12}$	305		460.56	340.05	707.56	
	0.5	$[^2H_6]Me_2CO$	305					379.30
1-CH_2OCH_3, 2-OCH_3	0.5	$CCl_4 + C_6D_{12}$	305		439.01	334.02		382.29
	0.5	$[^2H_6]Me_2CO$	305		443.09	335.23		

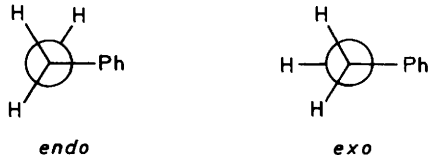
[a,b] See footnotes *a* and *d*, Table 2. Standard deviations of chemical shifts are *ca.* 0.05 Hz. [c] The ambient probe temperature, Varian HA-100. [d] Estimated standard deviation dependent on the width of peaks. [e] Deceptively simple AB_2 system.

to methylation of the phenolic hydroxy group. However, some qualitative deductions can be made. First, the difference $\nu_6 - \nu_4$ of (**1**) in D_2O suggests that the system is not *open*. This chemical shift difference is sensitive to the *open* $\rightleftharpoons$ *clsd1* equilibrium.[4] The chemical shift of 5-H is not conformationally dependent, as shown by the linear concentration dependence in $[^2H_6]Me_2CO$–CCl_4 and can thus be used as an internal standard.[4] The difference $\nu_3 - \nu_5$ seems to be sensitive only to the conformation of the 2-hydroxy or 2-methoxy groups. It is sensitive to solvation of the hydroxy group and comparisons can be done only for the same kind of solvents. A comparison with the value for (**5**) in dioxane (−9.74 Hz, corresponding to *ca.* 60% *open*) and CCl_4 (5.66 Hz, 90% *clsd*) suggests that the conformation of 2-OH in (**1**) in D_2O (−4.67 Hz) is probably *ca.* 50% *open*. This indicates that a structure with $\psi_1 = \psi_3 = 0°$ is present due to hydration of the hydroxys.

The Conformation of the CH_2OH *Sidechain.*—Some $^3J(CH_2,OH)$ values are reported in Table 7 and were measured in CCl_4 and $[^2H_6]$acetone. A concentration dependence in CCl_4 was observed, but the value at 0.1% approximates to infinite dilution.[3] The observed values range from 5.50 [(**1**) in acetone] to 7.02 Hz [(**6**) in CCl_4)]. In the literature, $^3J_{anti}$ in the corresponding alcohols is given as 11—12 Hz and $^3J_{gauche}$ as 2—3 Hz.[12] For the two conformations of the hydroxy group, termed *exo* and *endo*,[3] the average couplings should thus be 6.5—7.5 and 2—3 Hz. The observed value of ^3J in 2,6-dimethoxybenzyl alcohol (**6**) is 7.022 Hz, so that the value of $^3J_{exo}$ is at least that. Because ^3J in (**6**) is clearly affected by acetone, we assume that (**6**) in CCl_4 is not completely in the *exo* form and that $^3J_{exo} = 7.5$ and $^3J_{endo} = {}^3J_{gauche} = 2.5$ Hz. The resulting populations of the *endo* form vary from 60 to 95%. The estimates are sensitive to the structure of the *endo* isomers,[25] for which the dihedral ψ_2 may change from molecule to molecule.

The solvent effect of acetone is very clear and systematic; the *exo*-form is favoured, probably due to steric effects.

About the Energetics of the Hydrogen Bonds; Hydroxy Chemical Shifts.—The relation between the hydroxy proton chemical shift and the strength of the hydrogen bond is well documented.[2,26,27] Schaefer[27] has suggested the relationship $E = 4.2\,\delta_{OH} + 0.8$ (in kJ mol^{-1}) where δ_{OH} is the OH chemical shift with reference to phenol (δ 4.29), and E is the hydrogen-bond energy. Similarly, there is relationship between stretching frequency and the enthalpy of formation of the hydrogen bond.[3,28] The phenolic hydroxy proton chemical shift in (**1**) (δ 6.98, Table 7) is large, for example, in comparison with that of 2-methoxyphenol (δ 5.41[29]) and (**5**) (δ 5.70). The same trend is seen in the stretching frequencies for phenol, (**1**), (**2**), and 2-methoxyphenol:[2] 3 612, 3 440, 3 426, and 3 558 cm^{-1}. The chemical shift relation suggests that the energies of formation of the hydrogen bonds of (**1**) and (**2**) are as large as 12 kJ mol^{-1}. For (**2**) the free energy difference between the *clsd* and *open* forms is only *ca.* 6 kJ mol^{-1}.[5] This is explained by an entropy of 20 J K^{-1} mol^{-1}, which can be accounted for by relatively free rotation of the CH_2OR group. The numbers and the explanation are in a good agreement with the dynamic model for (**2**), for which a hydrogen bond energy of 10 ± 1 kJ mol^{-1} is suggested.[5]



The n.m.r. data for (**5**) in Table 5 show that the free energy of the hydrogen bond between the hydroxy and the *ortho*-methoxy groups is bigger than that to *ortho*-CH_2OH, although the chemical shifts imply the opposite. The fractions of *clsd1*, *clsd2*, and *open* type conformers in benzene as derived on the basis of the previous data are 0.15, 0.54, and 0.31, respectively. This can be accounted for by the co-operative effect of the $CH_2OH \cdots O(2)$ hydrogen bond and for the entropy reasons described above. The spectrum is completely analysable only in benzene; in other solvents the spin system is too complex.

However, ^6J(OH,6-H) is large in all the solvents and shows that the system is not sensitive to solvent, as expected.

The nature of the *clsd2* form is interesting in the light of the available hydroxy i.r. and chemical shift data. The CH_2OH hydroxy chemical shifts are all δ *ca.* 1.6—2.0 for the present salicyl alcohol derivatives. The differences from that of benzyl alcohol (1.1 p.p.m.) are small and may be accounted for partly by substituent effects.[30] Also, the corresponding i.r. frequencies are very close to that of benzyl alcohol. These observations, as well as the STO-3G calculations, suggest strongly that the hydrogen bond in *clsd2* is weak. On the other hand, a hydrogen bond between CH_2OH and the *ortho*-methoxy group is clearly indicated by the i.r. method in some αα-dialkyl derivatives of (**4**)[19] and should thus be possible in the present systems. Also, the OH–ring hydrogen bond can be very clearly seen by the direct methods, for example, in some rigid β-arylethanols,[31] in which the hydroxy group is in an optimal position with respect to the ring. Because all the present data show that the *clsd2* form is only a few kJ mol^{-1} less stable than the *clsd1* form, to solve the dilemma and to show that the three-site model is correct we should explain why the i.r. and hydroxy group chemical shift methods fail in this case. We do this as follows. First, the OH–O angle in the *clsd2* form is smaller (180°) and thus the electric field effect on the HO bond is not as large as it is, for example, in *clsd1*. Furthermore, the hydrogen bonding in *clsd2* involves overlap with the oxygen p_z orbital instead of a pure sp^2-lone pair and it may be assumed that this kind of bond is weak and mainly a dipole–dipole-type interaction. Second, even though probably weak, the OH • • • π interaction strengthens the *clsd2* structure, but is not seen for the same reasons as above: the electric field in the OH-direction is weak and the electric field of the π-system compensates for part of the field in the H • • • O direction. If the effects of the hydrogen bonding on i.r. frequencies and hydroxy chemical shifts are assumed to be caused mainly by the electric field in the OH direction, these effects are not in this case as large as they are in the more common cases used to derive the correlations between i.r. frequencies and hydrogen bond strengths. Third, the observed hydroxy chemical shift with reference to that of benzyl alcohol includes conformational and substitutional contributions which cannot be easily estimated and separated from each other.

An interesting piece of information is available for 2,6-dimethoxybenzyl alcohol (Table 6). $^3J(CH_2OH)$ implies that the system is almost completely in the *endo* form. ^6J in CCl_4 is bigger than that in acetone, in which it nearly corresponds to $\psi_1 = 90°$ (if ^6J follows the model given in ref. 5), indicating that ψ_1 in CCl_4 is not equal to 90°. This means that the CH_2OH group tilts between the two *clsd2* type conformations, separated by a shallow barrier. As for the possible CH_2OH • • • π-interaction, it should be possible in (**6**) if anywhere. The large $^3J(CH_2OH)$ and the small ^6J rule out the structure with ψ_3 0 and ψ_1 90°. Anyway, the data clearly show a total interaction, which favours the *endo* form, and it is quite possible that it is composed of nearly equal CH_2OH–methoxy and CH_2OH–π-system interactions.

Conclusions

The conformations of the present salicyl alcohols and of 2-fluorobenzyl alcohol[22] are statistically well described by a three-site model. The most stable conformer is *clsd1*, with a phenolic hydrogen atom bonded to CH_2OH oxygen atom. In the second well characterized conformation, called *open*, there are no hydrogen-bonding interactions and CH_2OH rotates rather freely about the ring plane. The 'principal site analysis', as well as the behaviour of (**4**) and (**6**) and the comparison of the coupling data of (**1**) and (**2**), indicate that there exists a conformer, named *clsd2*, in which a hydrogen bond exists between the CH_2OH hydroxy group and the phenolic oxygen atom. This form is not indicated clearly by the i.r. and hydroxy chemical shift probes.[1,3] On the basis of the STO-3G calculations (Table 1) the *clsd2* form is relatively rigid. The presence of the *clsd2* form can be partly explained by an interaction between the hydroxy group and the π-system and by the minimum interaction between the CO bond and the ring, as also suggested for benzyl alcohol and benzyl fluoride.[9,10] The energy difference between the *open* and the other forms is compensated greatly by the entropic freedom of the *open* form.

One should note that the results of 'principal site analysis for combined n.m.r. data' must be carefully studied before making any conformational conclusions. The approach is analogous to principal component analysis and the meanings of the molar fractions and spectral parameters may in some cases be mixed with substituent effects.

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References

1 J. M. Bakke and G. B. Lorentzen, *Acta Chem. Scand.*, 1974, **B28**, 650.
2 M. Takasuka and Y. Matsui, *J. Chem. Soc., Perkin Trans. 2*, 1979, 1743.
3 R. J. Abraham and J. M. Bakke, *Tetrahedron*, 1978, **34**, 2947 and references given therein.
4 R. Laatikainen, *Magn. Reson. Chem.*, 1986, **64**, 588.
5 R. Laatikainen and K. Tuppurainen, *Magn. Reson. Chem.*, 1986, **64**, 595.
6 M. Oki and H. Iwamura, *Bull. Chem. Soc. Jpn.*, 1959, **32**, 950, 595.
7 M. Oki, H. Iwamura, and I. Urushibara, *Bull. Chem. Soc. Jpn.*, 1958, **31**, 796.
8 T. Schaefer, W. Danchura, W. Niemczura, and W. J. E. Parr, *Can. J. Chem.*, 1978, **56**, 1721.
9 M. Traetteberg, H. Ostensen, and R. Seip, *Acta Chem. Scand.*, 1980, **A34**, 449.
10 R. J. Abraham, R. A. Hearmon, M. Traetteberg, and P. Bakken, *J. Mol. Struct.*, 1979, **57**, 149.
11 T. Schaefer, J. Peeling, and R. Sebastian, *Can. J. Chem.*, 1985, **63**, 3219.
12 R. R. Fraser, M. Kaufman, P. Morand, and G. Govil, *Can. J. Chem.*, 1969, **47**, 403; C. P. Rader, *J. Am. Chem. Soc.*, 1969, **91**, 3248.
13 M. Oki and H. Iwamura, *Bull. Chem. Soc. Jpn.*, 1959, **32**, 567; M. Traetteberg and H. Ostensen, *Acta Chem. Scand.*, 1979, **A33**, 491.
14 R. K. Bly and B. S. Bly, *J. Org. Chem.*, 1963, **28**, 3165; M. Tichy, *Adv. Org. Chem.*, 1965, **5**, 115; M. Oki, H. Iwamura, T. Onada, and M. Iwamura, *Tetrahedron*, 1968, **24**, 1905.
15 R. J. Abraham and J. M. Bakke, *Acta Chem. Scand.*, 1981, **B35**, 367.
16 R. J. Abraham and J. M. Bakke, *Acta Chem. Scand.*, 1983, **B37**, 865.
17 R. J. Abraham and J. M. Bakke, *Acta Chem. Scand.*, 1984, **B38**, 547.
18 J. L. Pierre and R. Perraud, *Tetrahedron Lett.*, 1973, 1935; M. Oki and H. Iwamura, *ibid.*, p. 4003.
19 A. Yamashita, K. Hara, S. Aizawa, and M. Hirota, *Bull. Chem. Soc. Jpn.*, 1974, **47**, 2508.
20 V. Kral, R. Laatikainen, and Z. Arnold, *Tetrahedron*, 1985, **41**, 4919.
21 T. Schaefer and R. Sebastian, *J. Magn. Reson.*, 1980, **41**, 395.
22 T. Schaefer and W. J. E. Parr, *J. Chem. Phys.*, 1976, **65**, 1197.
23 V. Balevichius and L. Kimptys, *Org. Magn. Reson*, 1977, **9**, 489; 1976, **8**, 180.
24 R. Laatikainen and V. Kral, *J. Chem. Soc., Perkin Trans. 2*, 1985, 1091.
25 R. Laatikainen, S. Lõtjõnen, and P. Äyräs, *Acta Chem. Scand.*, 1980, **A34**, 249.
26 D. P. Eyman and R. S. Drago, *J. Am. Chem. Soc.*, 1966, **88**, 1617.
27 T. Schaefer, *J. Phys. Chem.*, 1975, **79**, 1888 and references cited therein.
28 R. S. Drago and T. D. Epley, *J. Am. Chem. Soc.*, 1969, **91**, 2882.
29 T. Schaefer and T. A. Wildman, *Can. J. Chem.*, 1979, **57**, 450.
30 R. J. Abraham and J. M. Bakke, *Org. Magn. Reson.*, 1980, **14**, 312.
31 H. Iwamura, *Tetrahedron Lett.*, 1970, 2227.

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