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Variable-Temperature NMR Studies of 2,6-Dihydroxy Acylaromatic Compounds. Deuterium Isotope Effects on Chemical Shifts, Isotopic Perturbation of Equilibrium and Barriers to Rotation

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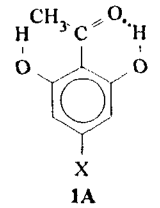
A series of 2,6-dihydroxy acylaromatic compounds were investigated to characterize the rotational and hydrogen bonding properties of the carbonyl group. Deuterium isotope effects on ^{1}H and ^{13}C chemical shifts due to deuteriation of OH groups were determined at both ambient and low temperature. In the latter case isotope effects on chemical shifts of the individual rotamers can be determined. Deuteriation of one of the OH groups may lead to isotopic perturbation of the tautomeric equilibrium of the carbonyl group and the two hydroxyl groups. The perturbation was found to be larger in ketones than in esters. Complete band shape analysis of the OH resonances of the esters and ketones in a temperature interval above and below the coalescence temperature led to $\Delta G^{\neq}$, $\Delta H^{\neq}$ and $\Delta S^{\neq}$ values for various concentrations of added THF-d_8. $\Delta S^{\neq}$ was found to be strongly negative. Temperature coefficients for the shift of the OH resonances showed large variations for esters and ketones owing to the different hydrogen bond patterns. The esters have two intramolecular hydrogen bonds, one strong and an additional weaker one between the OH and OR groups. The second OH group of the ketones was shown to point primarily towards C-5. Increasing amounts of THF-d_8 increased the amount of this rotamer. The anisotropy of the XC=O group at C-2, C-6 was shown to lead to a low-field shift of C-2, very different from that found for C=O groups without hydrogen bonds. The anisotropy caused by OH groups can also be estimated. On the basis of the thermodynamic parameters, a model for the rotation of the ester group is suggested. The rate-determining step involves both intramolecular hydrogen bonds, which are twisted out of the ring plane to form hydrogen bonds to the solvent or other hydrogen bond acceptors.

KEY WORDS ^{13}C NMR Deuterium NMR isotope effects Rotational barriers *o*-Hydroxy acylaromatics Isotopic perturbation of equilibrium Band shape analysis

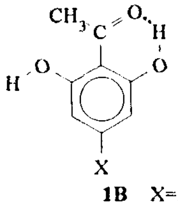
INTRODUCTION

2,6-Dihydroxy acylaromatics have attracted much interest since the first inventive variable-temperature NMR studies by Koelle and Forsén.[1] This group of compounds (**1**–**5**) constitute a model for studies of inter- and intramolecular hydrogen bonding. Further, a possibility exists of freezing out the rotamers of the carbonyl group. Measuring the strength of the internal hydrogen bond is a central problem.[2–10] IR data[2–4,9] have been correlated with the strength of intermolecular hydrogen bonds but similar correlations for intramolecular hydrogen bonds are less common. Based partly on the work of Gränacher,[11] Schaefer[12] found a correlation between δ_{OH} and the intramolecular hydrogen bond strength.

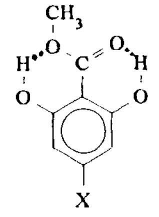
Koelle and Forsén[1] suggested that the height of the rotational barrier for C=O group rotation measured by $\Delta G^{\neq}$ or $\Delta H^{\neq}$ to a certain extent reflects the strength of the intramolecular hydrogen bond in this type of compound. By means of dynamic NMR they deter-



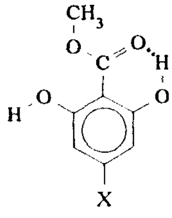
1A
2A



1B X=H
2B X=CH$_3$



3A
4A
5A



3B X=H
4B X=CH$_3$
5B X=OCH$_3$

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mined $\Delta G^{\neq}$, $\Delta H^{\neq}$ and $\Delta S^{\neq}$ for 2,6-dihydroxyacetophenone (**1**) and methyl 2,6-dihydroxybenzoate (**3**) dissolved in diethyl ether and $CHFCl_2$, respectively. The determination for the ketone is subject to great uncertainty because only signals above the coalescence temperature were used to evaluate the activation parameters and $\Delta\nu$ was taken from a low-temperature spectrum in which the OH signals are separated, but show exchange broadening. Koelle and Forsén[1] found a marked decrease in the barrier on changing to solvents with greater hydrogen bonding ability, but no systemic study of solvent effects has been reported.

Several attempts have been made to determine the activation parameters. Antypas *et al.*[13] determined $\Delta H^{\neq}$ for **1** and 2,4,6-trihydroxyacetophenone in acetone and Hirota *et al.*[14] determined $\Delta H^{\neq}$ and $\Delta S^{\neq}$ for **3** in $CDCl_3$, but they only used data points above or near the coalescence temperature. No consistent set of $\Delta G^{\neq}$, $\Delta H^{\neq}$ and $\Delta S^{\neq}$ parameters has been presented and the great variation in the conditions used reflects the difficulty of investigating this class of compounds, primarily owing to their low solubility in solvents in which the rotation can be slowed sufficiently.

Deuterium isotope effects in *o*-hydroxyacyl compounds have been studied.[5,6,8,10] Studies of the symmetrical compounds **1**–**5** revealed an isotopic perturbation of the carbonyl group equilibrium for the monodeuteriated species, leading to an additional splitting of the C-2, C-6 and C-3, C-5 resonances. Splittings caused by isotopic perturbation of equilibrium, Δ_{SIP}, were previously analysed only in terms of a change in chemical shifts.[6] For the C-2, C-6 case this approach is too simple. For the C-3, C-5 value an evaluation of the OH rotamer populations has to be considered. Further, the factors determining the isotopic perturbation need further investigations. The slowing of the carbonyl group rotation at low temperature also allows a determination of the chemical shift anisotropy of this group. These anisotropies may be compared with values obtained from solid-state spectra. By means of solid-state and low-temperature NMR experiments the anisotropy of non-hydrogen-bonded carbonyl groups have been investigated.[15,16]

In low-temperature experiments on unsymmetrically substituted benzaldehydes, Drakenberg *et al.*[15] found that a carbonyl group has a shielding effect on C-2 when the carbonyl group is *cis* to C-2. Penner and Wasylishen[16] found that the anisotropy effect of a hydroxy group is rather small as determined by solid-state NMR. A study of isotopic perturbation of equilibrium[6] indicates that the anisotropy effect of XC=O groups in intramolecular hydrogen-bonded molecules is different from that found by Drakenberg and co-workers.[15,17]

In this work, the interplay between intramolecular and solvent intermolecular hydrogen bonds was studied by combining a number of parameters: deuterium isotope effects on chemical shifts, isotopic perturbation of equilibrium, chemical shifts and barriers to rotation. The possibility that the rotation of the C=O group may be slowed to observe parameters for the individual rotamer permits studies of isotopic effects on the chemical shifts of both intramolecular and intermolecular hydrogen-bonded OH groups as represented by 2-OH and 6-OH. The latter possibility is a rare case as non-hydrogen-bonded OH groups normally exchange too fast for isotope effects to be measured.

RESULTS

A series of compounds **1**–**5** were investigated. NMR measurements were made in CD_2Cl_2, in mixtures of CD_2Cl_2 and THF-d_8 or in pure THF-d_8. As can be seen from Tables 1 and 3, not all compounds were measured in all solvents, primarily because of solubility problems. Because of the low solublity of the ketones in CD_2Cl_2 at low temperature, the study of **1** in pure CD_2Cl_2 was carried out at relatively low concentration (0.01–0.05 M). All other samples had a concentration of 0.5 M, except when concentration effects on rotation were studied. In addition, not all compounds give useful data in all solvents either because their rotation rates are unfavourable at the given temperature or because of intermolecular exchange. Intermolecular OH exchange is observed to some extent at ambient temperature or higher. THF-d_8 has an enhancing effect on the exchange and for **3** in THF-d_8 exchange has been observed at temperatures as low as 235 K. The intermolecular OH exchange causes problems in the study of small splitting owing to isotopic perturbation of equilibrium. The intermolecular proton exchange was estimated to be about 20 s^{-1} at 270 K for **3** in THF-d_8 while the intramolecular rotation of the ester group was about 10^5 s^{-1} at 160 K.

The assignment of the ^1H and ^{13}C resonances was assisted by comparison with the ^1H and ^{13}C data for model compounds such as 2-hydroxy-6-methoxyacetophenone[8] and 2-hydroxy-4,6-dimethoxyacetophenone.[8] Most of the resonances were unambiguously assigned with the help of substituent effects, isotope effects and chemical shifts for model compounds, except for the sets of nuclei, which have different chemical shifts at low temperature. To make the assignments in the slow exchange limit, a COLOC experiment[18] was carried out at 200 K. From this experiment the resonances of C-2 and C-6 are unambiguously assigned via the two-bond C–OH couplings. The OH resonance of the hydrogen-bonded OH group resonates at lowest field (Table 1). Hydrogen bonding has a deshielding effect on C-2. It is still not possible to assign C-3/C-5 and H-3/H-5. The assignments of the OH resonances are given in Table 1 and the ^{13}C data are given in Table 2.

The ability to follow proton resonances from the slow exchange limit at low temperature to the rotationally averaged spectrum at higher temperature is determined by the coalescence temperature and the temperature interval between these limits. The range of this temperature interval is found to be about 100 K. The coalescence temperature is lowered when the concentration of the THF-d_8 is increased, which indicates that the barrier to carbonyl rotation is also lowered. The coalescence temperatures are listed in Table 1. The coalescence temperatures are in general lower for the esters than for the ketones when THF-d_8 is present in the solution. From Table 1 it is also evident that a

Table 1. ^{1}H NMR data for 1–5 and activation parameters

Compound	THF-d_8(%)[a]	Concentration (M)	Coalescence temperature (K)	OH shift at greatest separation: OH_{bound} (ppm)	OH_{free} (ppm)	Hz	Temperature (K)	Temperature gradient (Hz K^{-1})	Activation parameters: $\Delta G^{\neq}$ (kJ mol^{-1})[b]	$\Delta H^{\neq}$ (kJ mol^{-1})	$\Delta S^{\neq}$ (J mol^{-1} K^{-1})
1[c,d]	0	0.05[e]	220	13.32	6.75	1645	206	1.15[f]	40.6	27.4	−44.3
	8.3	0.5	197–206	13.43	10.26	795	169	1.40	41.5	24.5	−57.0
	50	0.5	169–178	13.64	10.53	778	163	1.28	37.2	22.7	−48.6
	100	0.5	169–178	13.76	10.64	780	155	1.23	35.5	25.3	−34.4
2	8.3	0.5	238–250	13.99	10.15	960	206	1.29	47.4	28.6	−63.0
3[g]	0	0.5	233	11.07	8.59	620	196	0.30	45.6	31.8	−46.3
	1.6	0.5	196	11.10[h]	8.67[h]	609[h]	155	0.34	43.0	20.9	−74.2
	3.2	0.5	178	11.05[h]	8.75[h]	580[h]	164	0.37	41.1	18.9	−74.5
	8.3	0.5	160–169	11.21[h]	8.97[h]	560[h]	142	0.61	40.5	16.3	−81.3
	50	0.5	<150	—	—	—	—	0.74	35.3	12.7	−75.6
	100	0.5	<150	—	—	—	—	1.05	28.0	17.7	−34.9
4[i]	0	0.5	238–247	10.99	8.50	623	206	0.26	47.0	32.7	−48.2
	0	0.05	250	11.02	8.54	621	206	0.31	47.3	36.8	−35.0
5	0	0.5	263–275	11.23	8.62	653	227	0.25	51.2	42.2	−30.0

[a] Solvent CD_2Cl_2. 100% equals pure THF-d_8.

[b] Determined at 298 K.

[c] $\Delta G^{\neq}$, $\Delta H^{\neq}$ and $\Delta S^{\neq}$ where found to 34.6 kJ mol^{-1}, 25.9 kJ mol^{-1} and −29.2 J mol^{-1} K^{-1}, respectively, for a 64% deuteriated compound.

[d] The chemical shift of the CH_3 group changes from 2.64 to 2.88 ppm on going from pure CD_2Cl_2 to pure THF-d_8.

[e] Saturated solution.

[f] The value for **1** in CD_2Cl_2 shows a great change between 160 and 200 K. The change quoted is determined between 200 and 320 K. The value between 160 and 320 K is 2.43 Hz K^{-1}.

[g] $\Delta G^{\neq}$, $\Delta H^{\neq}$ and $\Delta S^{\neq}$ where found to 46.3 kJ mol^{-1}, 28.8 kJ mol^{-1} and −58.9 J mol^{-1} K^{-1}, respectively, for a 63% deuteriated compound.

[h] The value is uncertain because the OH resonance is exchange broadened.

[i] $\Delta G^{\neq}$, $\Delta H^{\neq}$ and $\Delta S^{\neq}$ where found to 47.4 kJ mol^{-1}, 32.1 kJ mol^{-1} and −51.6 J mol^{-1} K^{-1}, respectively, for an 82% deuteriated compound.

Table 2. ^{13}C chemical shifts[a] and Δ_{SIP} values

Compound	THF (%)[b]	C shift (ppm): C-1	C-2	C-6	Difference[c]	C-3[d]	C-5[d]	Difference[c]	C-7	Temperature (K)[e]	Δ_{SIP}: C-2/6	C-3/5	Temperature (K)[e]
1	0	110.48	161.52			108.43			205.46	304	—[f]	—[f]	—
	8.3	108.72	162.98	159.79	3.19	106.92	105.28	1.64	205.25	160	0.346	0.236	275
	50	108.79	163.29	160.05[g]	3.24	106.7[g]	105.6[g]	1.1[g]	204.85	160	0.363	0.243	201
	100	108.09	163.33	159.40	3.93	106.82	104.60	2.22	204.08	151	0.392	0.269	215
2	8.3	103.72	165.68	161.05	4.62	92.42	91.22	1.20	203.06	164	—[f]	—[f]	—
3	0	98.86	161.27	157.68	3.59	107.31	106.93	0.38	169.67	178	0.228	0.105	304
	1.6	98.48	160.9[g]	157.3[g]	3.57	106.8[g]			169.05	151	0.229[h]	0.109[h]	318[i]
	3.2	100.36	161.14			108.26			170.33	318	0.222[h]	0.078[j]	318
	8.3	98.71	160.9[g]	157.5[g]	3.40	106.65			169.41	140	0.226[h]	0.086[j]	304
	50	100.44	161.34			108.06			170.53	304	0.205	0.085[j]	304
	100	101.77	162.69			109.11			171.90	304	0.170[i]	0.127[h]	235
4	0	96.50	160.85	157.39	3.46	108.06	107.73	0.33	169.25	180	0.220[h]	0.082[j]	304
5	0	96.50	162.58	158.79	3.79	92.95	92.95	0.30	168.79	151	0.234[h]	0.058[j]	304

[a] Chemical shifts are referenced using CD_2Cl_2 (53.6 ppm), except for **1** and **3** in 100% THF-d_8, which are referenced to a trace of CH_2Cl_2 and THF-d_8 (67.9 ppm), respectively. The ^{13}C chemical shifts depend on temperature. See text.

[b] Solvent CD_2Cl_2. 100% equals pure THF-d_8.

[c] When no difference is quoted the frozen chemical shifts were not measured.

[d] Assignments are tentative (see text).

[e] The temperature used to determine the chemical shifts and the Δ_{SIP} values were often different (see text).

[f] No SIP value was measured.

[g] Values ±0.2 ppm.

[h] Values ±0.005 ppm.

[i] SIP values for C-3/C-5 were measured at 304 K.

[j] Only two peaks are observed owing to intermolecular exchange.

methoxy group in the 4-position will increase the coalescence temperature by about 30–40 K for both the ketone and the ester.

Chemical shifts

OH chemical shifts. The OH chemical shifts are key parameters in estimating hydrogen bond strengths and in the complete band shape analysis. Above the coalescence point only an averaged resonance for 2-OH, 6-OH is observed. The individual shift values were obtained for a number of compounds, as shown in Table 1. It turns out that both the absolute and the relative chemical shifts of the hydroxy protons change with temperature. An example is **2**, where the frequency difference between the hydroxy resonances is 915 Hz at 165 K and 960 Hz at 206 K. The free hydroxy proton

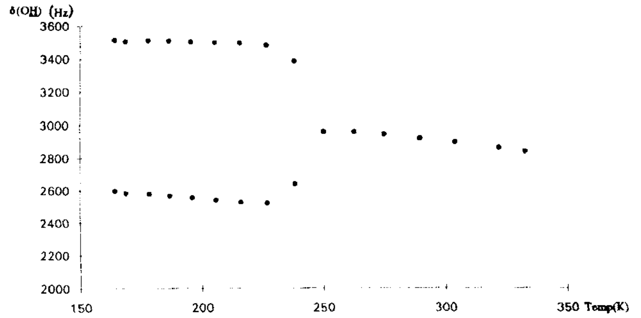

Figure 1. Plot of the ^{1}H chemical shifts at 250.13 MHz of the OH resonances of **2** in CD_2Cl_2 + 8.3% THF-d_8 at various temperatures.

shows the greatest change in shift with temperature (Fig. 1). The chemical shifts of the hydroxy protons given in Table 1 were taken at the temperature of greatest frequency difference between OH resonances. The average change, in Hz K^{-1}, for the exchange averaged chemical shift of the hydroxy proton at different THF-d_8 concentrations are given in Table 1. They are greater for the ketone than for the ester at low THF-d_8 concentrations, but they are nearly identical at 100% THF-d_8.

The resonance of the free OH group of **1** shows a sharp change in chemical shift below 190 K (Table 1). This feature could be related to dimerization, as also indicated by the low solubility of this compound at low temperatures. For **1** a tremendous downfield shift of the free hydroxy proton is found on going from pure CD_2Cl_2 to CD_2Cl_2 + 8.3% THF-d_8. This indicates that the free hydroxy proton forms an intermolecular hydrogen bond to THF-d_8.

H-3, H-5 chemical shifts. At low temperatures the chemical shift difference between H-3 and H-5 can be determined as a function of the orientation of the XC=O group and the intramolecular hydrogen bonding. No unambiguous assignments have been made. The ester shows a chemical shift difference between H-3 and H-5 of 0.037 ppm compared with a value for the ketone of 0.068 ppm in CD_2Cl_2. A methoxy group in position 4 increases these shifts differences to 0.046 and 0.134 ppm, respectively. Addition of the THF-d_8 also increases this difference, especially for the ketone. With 8.3% THF-d_8 added the value is 0.096 ppm. The difference in chemical shift between H-3 and H-5 is small. Use of these resonances for complete band shape analysis is therefore difficult owing to the corresponding low coalescence temperature.

^{13}C chemical shifts. The ^{13}C chemical shifts of the individual rotamers obtained at low temperature are given in Table 2. Isotopic perturbation studies suggested that of the C-2, C-6 pair, the C-2 was the one at high field.[6] A COLOC experiment[18] at low temperature (200 K) confirmed this suggestion for the esters. The chemical shift differences between C-2 and C-6 or between C-3 and C-5 depend to some extent on the solvent (Table 2). The chemical shift difference between C-2 and C-6 of **1** increases only slightly up to 50% THF-d_8 added, whereas a change of about 23% is found on going from 50% THF-d_8 in CD_2Cl_2 to pure THF-d_8 (Table 2).

The ^{13}C chemical shifts depends to a small extent also on temperature. C-2 (hydrogen bonded) varies by 2.60 Hz K^{-1} and C-6 by 0.45 Hz K^{-1}, as found in 2-hydroxyacetophenone. The large chemical shift difference between C-2 and C-6 in principle makes this set of resonances eligible for complete band shape analysis. However, in practice this is not so because of the difficulty of observing these resonances in a broad region around the coalescence point.

Isotope effects

$^n\Delta$C(D). Ambient temperature isotope effects for **1** and **4** have been reported several times.[6,8,10] Compound **1** in CD_2Cl_2 + 8.3% THF-d_8 gives for C-2/C-6 a slightly larger and for C-3/C-5 a smaller isotope effect than found in $CDCl_3$.[6,10] Isotope effects for **4** in CD_2Cl_2 are for C-2/C-6 in accordance with those found in $CDCl_3$ but for C-3/C-5 it is slightly larger.[6]

Examination of the ambient temperature isotope effects in various mixtures of CD_2Cl_2 and THF-d_8 provides interesting features (Fig. 2). The isotope effects on C-2/C-6 for **1** increase in magnitude as the concentration of THF-d_8 is increased, whereas the situation for **3** is more complicated, first a small increase and then a decrease being observed. The ketones show larger isotope effects than the esters, as reported previously.[6,8,10]

Low-temperature studies permitted the observation of isotope effects of the individual rotamers for the first time, as shown in Fig. 2. These low-temperature spectra show two- and three-bond isotope effects with aromatic carbons, but in not instances are four-bond isotope effects with these carbons observed. The two-bond isotope effects, $^2\Delta$C-2(OD), are distinctly larger in the ketones than in the esters and 4-methoxy substituents lead to a slight increase in comparison with the parent compounds, in good agreement with studies on model compounds.[8]

$^n\Delta$H(OD). Isotope effects across six bonds, $^6\Delta$H-6(2-OD), of the order of 0.006 ppm are observed in the low-temperature spectra of **3**. This is not the case for the acetophenones. Further, no $^6\Delta$H-2(6-OD) isotope effects were observed.

Temperature variation of isotope effects. Isotope effects on nuclear shielding are known to vary slightly with temperature.[19] The temperature variation for the isotope effects of 2-hydroxyacetophenone show that $^2\Delta$C-2, $^4\Delta$C-4 and $^4\Delta$C-7 increase at higher temperatures, whereas $^3\Delta$C-3 decreases, the coefficients being 1.2×10^{-4}, 6.6×10^{-5}, 1.25×10^{-4} and -8.1×10^{-5} ppm K^{-1}, respectively. Although small, this temperature dependence must be kept in mind when comparing isotope effects presented here and in the literature.

Isotopic perturbation of equilibrium

Monodeuteriation of the symmetrical compounds (**1**–**5**) leads to isotopic perturbation of equilibrium[6,10] (see Fig. 5). The observed splittings, Δ_{SIP}, are given in Tables

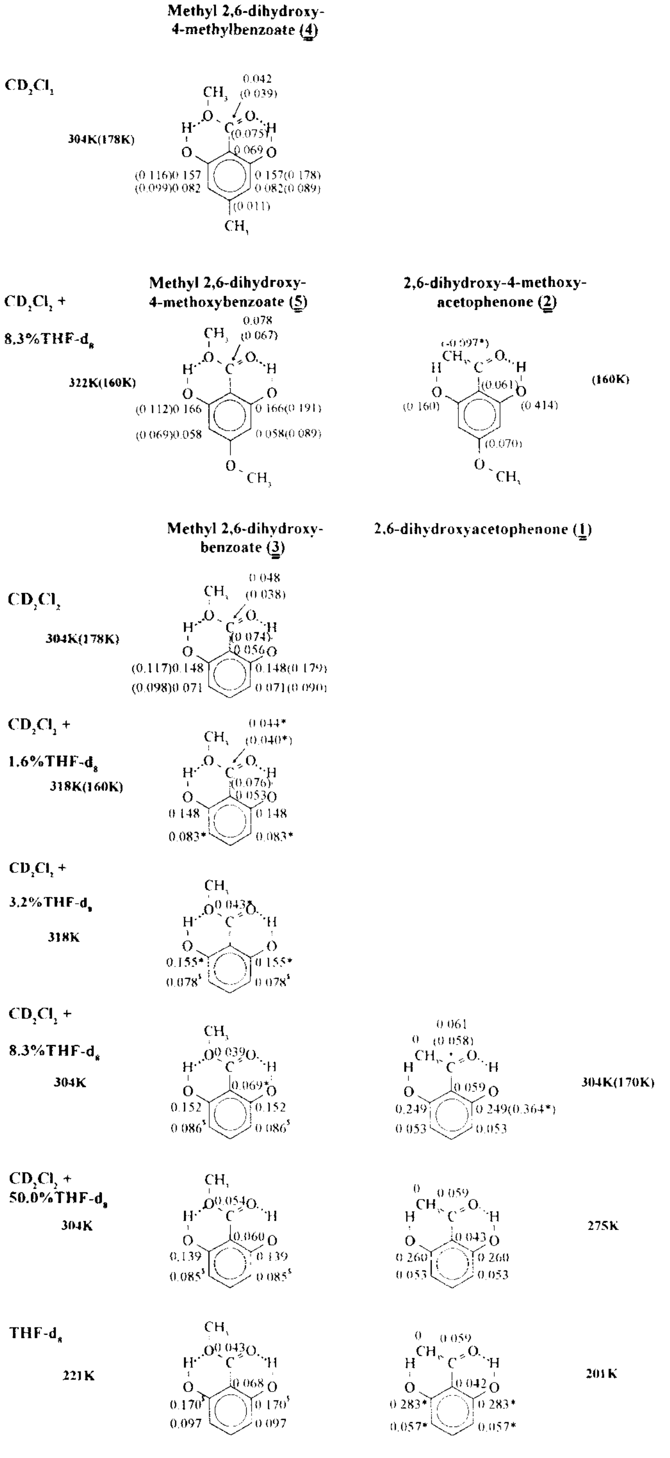

Figure 2. Isotope effects for compounds **1–4**; **1** and **3** in different mixtures of CD_2Cl_2 and THF-d_8. Low-temperature values in parentheses. * Uncertain values. $ Only two peaks are observed, indicating intermolecular exchange.

2 and 3. Different temperatures were used in order to be able to observe the effects. This is especially true for the compounds dissolved in a solvent mixture containing more than 50% THF-d_8. For **5** a temperature of 304 K was necessary and for **2** Δ_{SIP} values could not be obtained below the poiling point of the solvent (see Table 2). The difficulty of observing Δ_{SIP} values in solvent mixtures containing high percentages of THF-d_8 is due to intermolecular exchange.

Table 3. Fractions of isotopic perturbation, α, and Δ_{SIP}(OH)

Compound	THF-d_8 (%)[a]	Δ_{SIP}(OH) (Hz)	$\alpha - 0.5$ (%) ^1H	^{13}C	Temperature (K)
1	0	—	—	—	—
	8.3	14.73	1.85	1.65	304
	50	13.11	1.69	1.72[b]	275
	100	14.04	1.80[b]	1.49[b]	250
3	0	6.94	1.12	1.16	304
	1.6	7.25	1.17	1.18[b]	304
	3.2	—	—	1.00[c]	318
	8.3	7.94	1.28[c]	1.14[b]	304
	50	5.65	1.01[c]	1.08	304
	100	—	—	0.00[b]	235
4	0	6.85	1.10	1.15[b]	322
5	8.3	7.96	1.22	0.94[b]	322
	15.4	8.29	1.27	—	322

[a] Solvent CD_2Cl_2. 100% equals pure THF-d_8.
[b] Uncertain because of noise.
[c] Uncertain because the frozen shift difference is estimated.

The Δ_{SIP} values for C-2/C-6 and C-3/C-5 are seen to vary with the type of compound and with the solvent. They increase for the ketone with increasing amount of THF-d_8. For the ester an irregular pattern is found.

The perturbation of equilibrium is also visible in the ^1H spectra. Here deuteriation results in an extra OH resonance from the monodeuteriated species. Variation of the degree of deuteriation reveals that the resonance at low field is due to the monodeuteriated species.[6,10] These splittings are given in Table 3. Intermolecular OH exchange is observed in some cases. To obtain the true SIP value a range of temperature should be investigated to ensure that no exchange is taking place.

The difference in chemical shift between the non-deuteriated and monodeuteriated species is a measure of the difference in the equilibrium between the two rotamers of each species, as described below. For ^1H spectra this splitting can be expressed as

$$\delta_{av}^{HD} - \delta_{av}^{HH} = [\alpha\delta_b + (1-\alpha)\delta_f] - [0.5\delta_b + (1-0.5)\delta_f] \tag{1}$$

where α is the fraction of the mono-deuteriated rotamers with OH hydrogen bonded and δ is the chemical shift of the hydrogen-bonded (b) and free (f) OH proton. This equation can be rearranged to give

$$\alpha = \frac{\delta_{av}^{HD} - \delta_{av}^{HH}}{\delta_b - \delta_f} + 0.5 \tag{2}$$

The intrinsic isotope effects complicate the picture of perturbation in the ^{13}C spectra and intrinsic isotope effects have to be taken into account. Δ_{SIP} can be expressed as

$$\begin{aligned}\Delta_{SIP(C\text{-}2,\,C\text{-}6)} = \delta^{HD} - \delta^{DH} &= \alpha[\delta C(H)_2 + {}^4\Delta C\text{-}2] \\ &+ (1-\alpha)[\delta C(H)_6 + {}^4\Delta C\text{-}6] \\ &- [(1-\alpha)\delta C(D)_2 + \alpha\delta C(D)_6]\end{aligned} \tag{3}$$

where α is the fraction of the monodeuteriated species with OH hydrogen bonded. Rearrangement and setting $1 - \alpha = \alpha$ for the small Δ terms, we obtain

$$\Delta_{\mathrm{SIP(C\text{-}2,\,C\text{-}6)}} = (2\alpha - 1)[\delta\mathrm{C(H)}_2 - \delta\mathrm{C(H)}_6] + \alpha({}^2\Delta\mathrm{C\text{-}2} + {}^2\Delta\mathrm{C\text{-}6} + {}^4\Delta\mathrm{C\text{-}6} + {}^4\Delta\mathrm{C\text{-}2}) \tag{4}$$

The frequency difference between resonances from the non-deuteriated and the doubly deuteriated species is given as

$$\delta^{\mathrm{HH}} - \delta^{\mathrm{DD}} = 0.5({}^2\Delta\mathrm{C\text{-}2} + {}^2\Delta\mathrm{C\text{-}6} + {}^4\Delta\mathrm{C\text{-}2} + {}^4\Delta\mathrm{C\text{-}6}) \tag{5}$$

Insertion of $\delta^{\mathrm{HH}} - \delta^{\mathrm{DD}}$ into Eqn (4) means that the degree of perturbation (α) can be formulated as

$$\alpha = 0.5\{1 + [(\delta^{\mathrm{HD}} - \delta^{\mathrm{DH}}) - (\delta^{\mathrm{HH}} - \delta^{\mathrm{DD}})]/[\delta\mathrm{C(H)}_2 - \delta\mathrm{C(H)}_6]\} \tag{6}$$

An error is made by averaging the isotope effects with 0.5 instead of α. This error can be minimized by solving Eqn (4) iteratively.

A similar set of equations can be formulated for C-3 and C-5 (see Discussion). Equations (2) and (6) lead to rotamer distributions as shown in Table 3. The agreement between ^{1}H- and ^{13}C-derived values is generally good and much better than found in Ref. 6. C-1 and C-7 in **3** and **4** in CD_2Cl_2 at low temperature split into four resonances. None of the other compounds show this pattern.

Rate constants

The rate constants for rotation of the carbonyl group are determined from complete band shape analysis of the OH resonances using the DNMR5 program.[20,21] Figure 3 shows a comparison between experimental and simulated spectra. We find rate constants from approximately 1 to 3×10^5 s^{-1} when the temperature is varied between 140 and 330 K, depending on the compound and the amount of THF-d_8. Rate constants for **3** in different mixtures of CD_2Cl_2 and THF-d_8 are shown in Fig. 4. All samples were followed on both sides of the coalescence temperature except for **3** in 1:1 CD_2Cl_2–THF-d_8 and pure THF-d_8. The logarithm of the rate constants fall on a straight line when plotted in an Eyring plot. The activation parameters obtained are presented in Table 1.

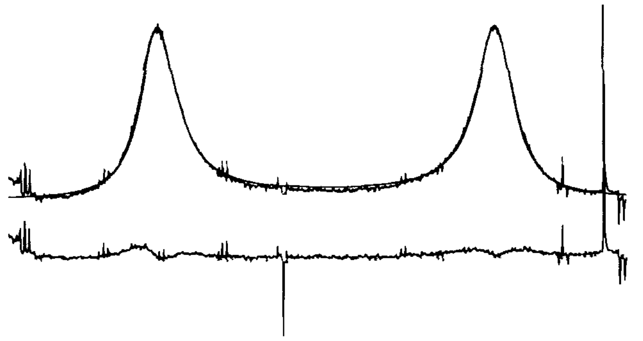

Figure 3. *OH* NMR spectrum of **3** at 216 K in CD_2Cl_2. Upper trace, experimental and simulated spectra; lower trace, difference spectrum between experimental and simulated spectra.

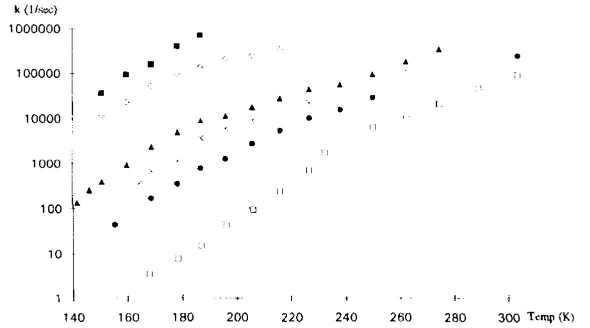

Figure 4. Rate constants for **3** in CD_2Cl_2 at various additions of THF-d_8. □ 0%, ● 1.6%, × 3.2%, ▲ 8.3% and ◇ 50% THF-d_8 in CD_2Cl_2 and ■ pure THF-d_8.

Earlier studies of activation parameters for this kind of molecule[1,13,14] were carried out in solvents other than CD_2Cl_2 and the THF-d_8 and in no case was the solvent dependence examined in detail. Two of these studies are based on analysis of spectra above or near the coalescence temperature.

Studies of **3** in $CHFCl_2$ [1] give nearly the same $\Delta G^{\neq}$ and $\Delta H^{\neq}$ values as found here in CD_2Cl_2 and also the value for $\Delta S^{\neq}$ (59.4 J mol^{-1} K^{-1}) is in reasonable agreement. On the other hand, studies in $CDCl_3$ [14] disagree with our results, but the former were based on only a few spectra obtained in a temperature interval of only 12 K.

Investigations of **1** in diethyl ether[1] give slightly smaller $\Delta S^{\neq}$ and $\Delta H^{\neq}$ values than found in THF-d_8. Likewise, values for $\Delta G^{\neq}$ and $\Delta S^{\neq}$ for **1** in acetone-d_6 [13] are in reasonable agreement with those found in THF-d_8.

We found nearly identical activation parameters for **3** and **4** and also between deuteriated and non-deuteriated species (Table 1). This indicates an uncertainty of *ca.* ±1 kJ mol^{-1} for $\Delta G^{\neq}$ and $\Delta H^{\neq}$ and ±2 J mol^{-1} K^{-1} for $\Delta S^{\neq}$ when our results are compared with one another.

The high concentration used in our experiments could promote self-catalysed intermolecular exchange. We therefore examined **4** at lower concentrations. The data for 0.5 and 0.05 M are compared in Table 1. No significant variation of the activation parameters is seen. A comparison of spectra at the same temperature but at different concentrations reveals a sharpening of the OH resonances when the concentration is decreased. This phenomenon has been observed previously for **3** in $CHFCl_2$.[1]

DISCUSSION

The central features of the compounds investigated are (i) the two OH groups, one of which is available for intramolecular hydrogen bonding and the other for either intermolecular or weak intramolecular hydrogen bonding, (ii) the internal rotation of the carbonyl group, (iii) the rate of this rotation and the barrier associated with this rotation and (iv) the orientation of the OH groups.

In order to analyse this situation, a number of parameters were investigated as discussed in the Results section.

Δ_{SIP} values

The splittings due to isotopic perturbation of equilibrium, Δ_{SIP}, constitute an interesting set of data as they depend on the change in equilibrium caused by deuteriation. They also depend on the difference in chemical shifts between the nuclei of the individual rotamers and for ^{13}C on the intrinsic isotope effects as shown in Eqn (6). This equation is more elaborate and more appropriate than the simple approach used in Ref. 6. Using the chemical shift differences determined at low temperature and the intrinsic isotope effects from the spectra above the coalescence point, the degree of perturbation of the equilibrium, α, can be calculated (Table 3).

A similar analysis can be made based on the splitting of the OH resonances [Eqn (2)]. The results from ^{13}C and ^{1}H data are similar although not identical. The data obtained from ^{13}C data are often less accurate owing to the low signal-to-noise ratios in these spectra, but most severely because intermolecular OH exchange may lead to too small Δ_{SIP} values.

It is seen from the results of Table 3 that the degree of perturbation is larger for ketones than for esters. This difference can be related to $\Delta G°$ and, as the change in $\Delta S°$ on deuteriation can be assumed to be small, the change in $\Delta G°$ is related to a change in $\Delta H°$. $\Delta H°$ refers to the difference in enthalpy between the two rotamers as shown in Fig. 5, one rotamer with an intramolecular hydrogen bond to deuterium and the other with an intramolecular hydrogen bond to hydrogen. For the stronger intramolecular hydrogen bond, as found in the acetophenones, a larger degree of perturbation is observed. Similarly, a slightly larger perturbation is observed in the 4-methoxy derivatives compared with the unsubstituted compounds.

Δ_{SIP} values are also observed for C-3/C-5. As stated in the Results section, equations similar to those for C-2/C-6 can be formulated for this pair of carbons. The chemical shift differences between C-3 and C-5 given in Table 2 cannot be taken as the chemical shift of the individual rotamers, as discussed below. Further, no realistic α values can be obtained as the ratio of the rotamers of the 6-OH groups (**1A** and **1B**) may vary with temperature, solvent and type of compound.

^{13}C chemical shifts

The chemical shift anisotropy induced by the XC=O group can be measured from the low-temperature spectra (Table 2). The difference in chemical shift between C-2 and C-6 is *ca.*3.5 ppm, but increases slightly for **1** in pure THF-d_8. For the 4-methoxy derivatives the difference is larger than in the corresponding unsubstituted derivatives. It is the C-2 carbon that resonates at low field. This is clearly different from what is found for acetones and aldehydes without hydrogen bonds.[15–17] The different behaviour can be ascribed to the extensive electron relocalization in the hydrogen-bonded compounds due to resonance-assisted hydrogen bonding (RAHB).[22]

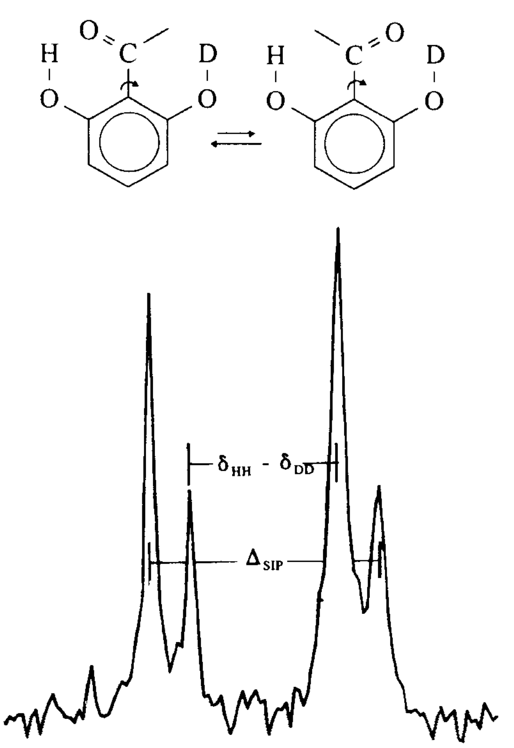

Figure 5. Monodeuteriated isotopomers and the ^{13}C NMR spectrum of C-2, C-6 illustrating the Δ_{SIP} splitting and the intrinsic, average isotope effect, $\delta^{HH} - \delta^{DD}$.

For the C-3, C-5 carbons the difference in chemical shift is smaller than for C-2, C-6, especially for the ester. This difference between C-3 and C-5 is probably not caused by anisotropy effects of the XC=O group, as no effects were seen in solution either in simple acetophenones or aldehydes,[17] although Penner and Wasylishen[16] observed a difference in solid-state studies of 4-nitroacetophenone of the order of 3.1 ppm. The difference is due, as suggested earlier,[6] to the orientation of the OH groups. The 2-OH bond due to the intramolecular hydrogen bond is clearly pointing away from C-3. The 6-OH group can take up various orientations according to the degree of intra- or intermolecular hydrogen bonding (**1A** and **1B**). In the ester a high degree of intramolecular hydrogen bonding to the OR group occurs (**3A**–**5B**), leading to both OH groups pointing in the same direction and hence explaining the smaller difference than for the ketones. For the ketone **1**, knowing the fraction of isotopic perturbation, α, a theoretical value of 4.9 ppm may be obtained for the chemical shift difference of the rotamer with the 6-OH group pointing towards C-5, using an equation similar to Eqn (6) (see also **1B**).

Isotope effects

The average two-bond isotope effect, $^{2}\Delta$C-2, C-6(OD), as observed at high temperatures, increases with increasing concentration of THF-d_8. As $^{2}\Delta$C-2(OD) is assumed to be insensitive to solvents or to decrease slightly,[8] the increase in the average can best be explained by an increase in $^2\Delta$C-6(OD) with increasing intermolecular hydrogen bonding. For **3** it is found that the three-bond isotope effects at C-3 and C-5, $^3\Delta$C-3(OD-2) and $^3\Delta$C-5(OD-6), are both larger than the average value. This can be explained by assuming small but negative long-range effects of the type$^5\Delta$C-5(OD-2) or $^5\Delta$C-3(OD-6). The isotope effects at C-1 are seen to increase at low temperature. For the long-range isotope effects a number of other interesting features are observed. The room temperature spectra show no isotope effect at the methyl carbon of the acyl group of **2**, although an isotope effects of *ca.* −0.1 ppm is seen at low temperature. In model compounds this isotope effects ranges from *ca.* −0.04 to −0.1 ppm.[8] The likely explanation is that the conformer without an intramolecular hydrogen bond gives a positive isotope effect and the average is therefore close to zero.

Temperature effects

The temperature changes of the OH chemical shift are related to the presence of non-hydrogen-bonded OH groups, as seen from the low-temperature data in Fig. 1. For the ketone, the temperature coefficient is large in CD_2Cl_2, but decreases with increasing amounts of THF-d_8 added. For the ester the trend is the opposite, as the second OH group of the ester in CD_2Cl_2 is hydrogen bonded to the OR group (see **3A–5A**).

Enthalpy of activation, $\Delta H^{\neq}$

$\Delta H^{\neq}$ for acetophenones is smaller than for esters in CD_2Cl_2, whereas the opposite is true in CD_2Cl_2–THF-d_8 mixtures (Fig. 6). The major difference between the esters and the ketones is the intramolecular hydrogen bond between 6-OH and the OR group in the former. This accounts for the relatively large $\Delta H^{\neq}$ in the ester. Second, for the acetophenones one would expect hydrogen bonding to add to $\Delta H^{\ddagger}$ compared with simple acetophenones. This stabilization is apparently offset by increased steric hindrance between the CH_3 and the 6-OH group, as pointed out by Hirota *et al.*[14]

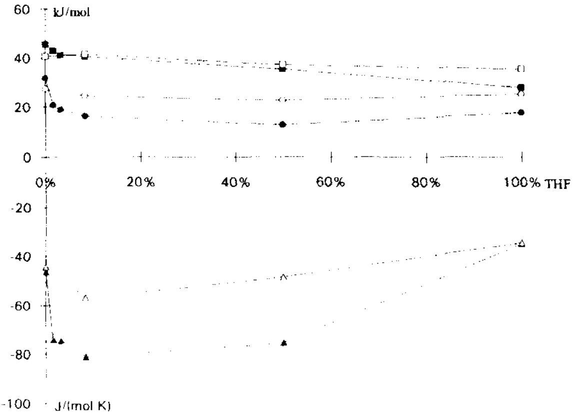

Figure 6. Plot of the variation of the activation parameters with the amount of THF-d_8. Open symbols, **1**; closed symbols, **3**. (□, ■) $\Delta G'$; (○, ●) $\Delta H'$; (△, ▲) $\Delta S'$.

On addition of THF-d_8 the $\Delta H^{\neq}$ value for the ester decreases as the intramolecular hydrogen bond between 6-OH and OR is broken, and finally increases slightly in pure THF-d_8.

Hydrogen bonding

The intramolecular hydrogen bond of 2-OH is firmly established using $^2\Delta$C-2(OD) isotope effects and OH chemical shifts. This hydrogen bond is not perturbed very much on addition of THF-d_8, as judged from the almost constant values of $^2\Delta$C-2(OD) and δ2-O*H*. The intramolecular hydrogen bond is much stronger in the ketone than in the ester and a methoxy group in position 4 strengthens the hydrogen bond. The interesting difference between the ketones (**1** and **2**) and the esters (**3**–**5**) lies in the behaviour of the 6-OH group.

Several pieces of evidence support the intramolecular hydrogen bond shown in **3A**–**5A**. The OH chemical shift is at low field compared with the ketone and is only slightly changed on addition of THF-d_8. Strong evidence is the observation of a deuterium isotope effect from 2-OD to 6-OH, an effect probably mediated via the hydrogen bonds and therefore not observed for the ketones. Further evidence is the small chemical shift difference between C-3 and C-5 (Table 2). As discussed above, this can be ascribed to the 6-OH group pointing primarily towards the OR group (**3A**–**5A**) and the much larger negative $\Delta S^{\neq}$ found for esters than for ketones shows that two hydrogen bonds are broken in the transition state. The low OH chemical shift temperature coefficient for the ester likewise indicates hydrogen bonding of both OH protons. This second hydrogen bond is of moderate strength as judged from δO*H* (Table 1). This hydrogen bond is interesting as it is an example of a non-resonance-assisted type. The 6-OH group of the ketones is typically pointing away from the methyl group, but not totally as the chemical shift difference between C-3 and C-5 is less than predicted (see earlier). The orientation with the OH group pointing away from the ester group is gradually favoured as more THF-d_8 is added. The chemical shift difference between C-3 and C-5 increases in **1**, a feature suggesting that the 6-OH rotamer with the 6-OH group pointing toward C-5 (**1B**) is increasing because of an increasing hydrogen bonding ability. The δ6-OH value in THF-d_8 (Table 1) points towards a reasonably strong intermolecular hydrogen bond.

Mechanism of rotation

The slight decrease in $\Delta H^{\neq}$ for **1** with addition of THF-d_8 shows that the 6-OH group is intermolecular hydrogen bonded in the ground-state. The considerably negative $\Delta S^{\neq}$ reveals that the hydrogen-bonded 2-OH group is hydrogen bonded to the solvent in the transition state. Both parameters thus support a mechanism for the ketone similar to that suggested by Antypas *et al.*[13] For the ester a much larger change in $\Delta S^{\neq}$ on addition of THF-d_8 indicates that the 6-OH group originally is intramolecularly hydrogen bonded and that both OH groups are hydrogen bonded to the solvent in the tran-

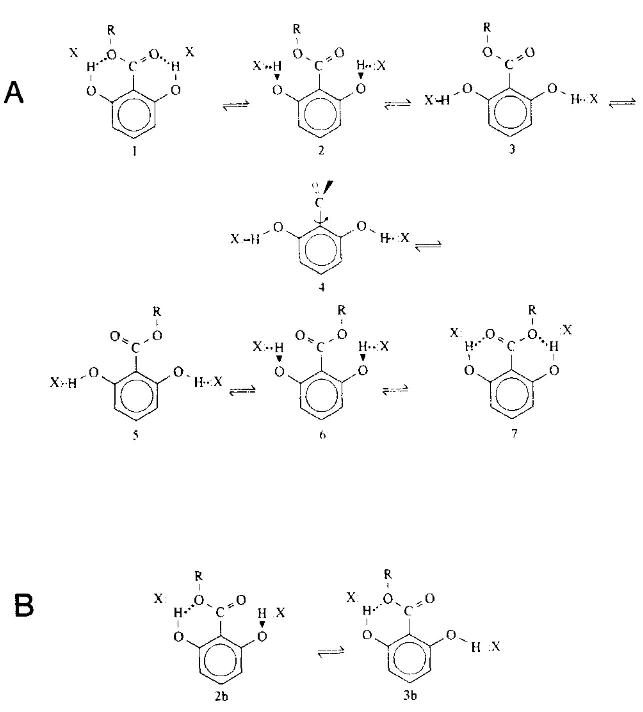

Figure 7. (A) proposed mechanism for the rotation of the ester group; X = solvent. (B) Alternative mechanism for step **2**–**3** (see text).

sitions state 2 as in Fig. 7. Breaking of the weaker hydrogen bond could possibly be occurring at a later stage as shown in **3b**$\rightleftharpoons$**4** (Fig. 7). However, this is not supported experimentally.

Addition of the THF-d_8 clearly decreases $\Delta H^{\neq}$ for both esters and ketones, thus facilitating rotation. The increase in $\Delta H^{\neq}$ observed for pure THF-d_8 is not fully understood.

Introduction of a methoxy group in the 4-position has an appreciable influence on the activation parameters. For both the ketone and the ester the rotation is slowed because of the substituent. This is in agreement with the resonance stabilization effect of the methoxy group.

We examined the influence of concentration on the rotation (Table 1). The variation of the activation parameters with concentration is of little practical importance.

CONCLUSIONS

Various parameters have been used in the discussion to obtain a picture of the ground state and the transition state of the symmetrical compounds **1**–**5**. The esters **3**–**5** are mainly in a conformation as shown in **3A**–**5A** with two intramolecular hydrogen bonds. This conformation becomes more populated at lower temperatures. On addition of THF-d_8 this fully intramolecular hydrogen-bonded structure is gradually changed into a structure with the 6-OH group hydrogen bonded to the solvent. The rotation process is facilitated by both OH groups forming hydrogen bonds to other species, e.g. solvent molecules. The ketones **1** and **2** form only one strong intramolecular hydrogen bond. The 6-OH group is primarily pointing away from the CH_3 group (**1B** and **2B**) and the amount of this rotamer increases on addition of THF-d_8. Intermolecular OH exchange is slow in CD_2Cl_2, but is catalysed by addition of THF-d_8.

EXPERIMENTAL

Compounds

2,6-Dihydroxyacetophenone (**1**), methyl 2,6-dihydroxy-4-methylbenzoate (**4**) and 2,4,6-trihydroxyacetophenone were purchased from Aldrich (Steinholm, Germany), methyl 2,4,6-trihydroxybenzoate from Lancaster (Mühlheim, Germany), 2-hydroxyacetophenone from Merck Schuchardt (Darmstadt, Germany) and methyl 2,6-dihydroxybenzoate (**3**) from Tokyo Kasei Kogyo (Tokyo, Japan). The 4-methoxy derivatives of **1** and **3** were prepared by methylation of the 2,4,6-trihydroxy derivatives with diazomethane and methyl iodide,[23] respectively. The isomers were separated by silica gel column chromotography wih *n*-hexane–chloroform–methanol (4 : 1 : 0.5) as the mobile phase.

Deuteriation of compounds

The deuteriated species were prepared by dissolving 0.25 mmol of the compound in 0.7 ml of methanol-d_1 and 0.3 ml of methanol. The ratio of methanol-d_1 to methanol was adjusted to obtain the desired degree of deuteriation. The degree of deuteriation was estimated for the ^1H NMR spectra.

Preparation of NMR samples

The concentrations used for the NMR experiments were 0.5 M except for **1** dissolved in CD_2Cl_2 (0.01–0.05 M). Compound **4** dissolved in CD_2Cl_2 was investigated at concentrations of both 0.5 and 0.05 M. Different ratios of CD_2Cl_2 and THF-d_8 were used (see Table 3).

NMR spectra

The ^1H and ^{13}C NMR spectra were recorded on a Bruker AC250 spectrometer operating of 250.13 and 62.9 MHz, respectively. The digital resolution for ^1H spectra was 0.13–0.63 Hz per point and for ^{13}C spectra 0.27 Hz per point. The chemical shifts are quoted relative to CD_2Cl_2 and $CHDCl_2$ for ^{13}C and ^1H, respectively. THF-d_7 was used as internal reference for **3** in THF-d_8 and **1** in THF-d_8 was referenced to traces of CH_2Cl_2.

For the COLOC spectra[18] the sweep width was 3496 Hz in F_1 (^1H) and 11904 Hz in F_2 (^{13}C). The 2D spectra were collected in 128 × 2048 data matrices and sine-bell apodization was used in the F_2 dimension. To improve the signal-to-noise ratio, 64 scans were measured for every increment. The digital resolution was 11.6 and 27.3 Hz in F_2 and F_1, respectively. The spectra were zero filled to 256 × 2048 data points before Fourier transformation.

The display temperature was calibrated by means of a methanol sample[24] and a Cu–CuNi thermocouple. The temperature is believed to be accurate to at least ±1 K.

Rate constants

Rate constants were determined by complete band shape analysis.[25] The complete band shape analysis was carried out with the DNMR5 program.[20,21] A good determination of the rate constant depends on the determination of $T_2{}^*$ and $\Delta\nu$. From the low-temperature spectra the chemical shift difference, $\Delta\nu$, between the *o*-hydroxyl proton resonances was found to be temperature dependent. The largest observed $\Delta\nu$ value was used in the complete band shape analysis for **3** in 1 : 1 CD_2Cl_2–THF-d_8 and THF-d_8 the $\Delta\nu$ value from **3** in CD_2Cl_2 + 8.3% THF-d_8 was used. $T_2{}^*$ was estimated from the line width of the OH resonance in the slow or fast exchange limits, as these signals have no contributions from the rotation process. For rotation-broadened signals the $T_2{}^*$ value were estimated by finding the ratio between $T_2{}^*$ of either a methyl or a methoxy resonance of a spectrum in both the sharp and the rotationally broadened temperature region and to multiply the $T_2{}^*$ value of a sharp OH resonance by this ratio.

Activation parameters

The enthalpy and entropy of activation were evaluated by a simple least-squares fit of ln (k/T) *vs.* $1/T$ points to a straight line (Eyring plot). The free energy of activation was evaluated by means of $\Delta G^{\neq} = \Delta H^{\neq} - T\Delta S^{\neq}$. The correlation coefficients (r^2) were between 0.945 and 0.998.

Acknowledgement

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