Isotopic Perturbation of Equilibrium in 2,6-Dihydroxybenzoyl Compounds. A ^{13}C and ^{1}H NMR Investigation*

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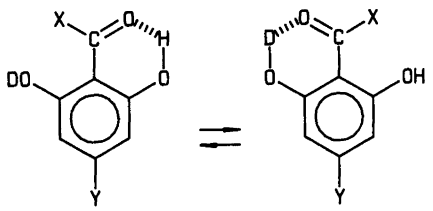
Deuterium isotope effects on ^{1}H and ^{13}C nuclear shielding of a series of 2,6-dihydroxybenzoyl derivatives have been studied. Isotopic perturbation of equilibrium is observed both in symmetric and asymmetric derivatives. It is shown that an OH group forms a stronger hydrogen-bond than an OD group. It is furthermore demonstrated that very extensive equilibrium isotope effects due to relay effects may be observed several bonds away from the center of isotopic substitution.

The anisotropy of XC=O groups in hydrogen-bonded systems is estimated and is shown to be quite different from that in non-hydrogen-bonded cases.

Isotopic perturbation of equilibrium has been used extensively in the study of carbonium ions.[1-3] Isotopic perturbation of equilibrium has also been observed in deuteriated 2,6-dihydroxyacetophenone[4] (**1**), yielding both the rotamer populations of the monodeuteriated species and an estimate of the "anisotropy" of the XC=O group.[4,5]

Furthermore, the study of intramolecular hydrogen-bonding and an evaluation of bond strength by means of $^{2}\Delta C(OD)$, as well as the directional dependence of $^{3}\Delta C(OD)$, has recently attracted much interest.[4-7] Long-range deuterium effects of carbonyl groups taking part in intramolecular hydrogen-bonds have also been reported.[4-7]



Scheme 1. Schematic representation of the HD isotopomers.

The present study includes also 2,6-dihydroxybenzoic acid ester derivatives such as methyl 2,6-dihydroxy-4-methylbenzoate (**2**), and the 3-bromo (**3**) and the 3,5-bromo (**4**) derivatives. These compounds allow a comparison of isotopic perturbation in a symmetric (**2** and **4**) and a non-symmetric (**3**) environment. A study of the ^{1}H NMR spectra of **1**–**4** leads to an estimate of whether an OH···O or an OD···O bond (see Scheme 1) is the strongest in these systems. The question concerning the strength of an O-H···O vs. an O-D···O hydrogen-bond has long been debated in its broadest sense.[8]

Deuterium substitution is shown to be a powerful means of studying symmetrical systems and also to detect subtle differences in e.g. rotamer distributions of nearly symmetrical compounds.

Results

^{13}C NMR data. The assignments for **1** and **5** (for structures, see Scheme 3) in dioxane are given by

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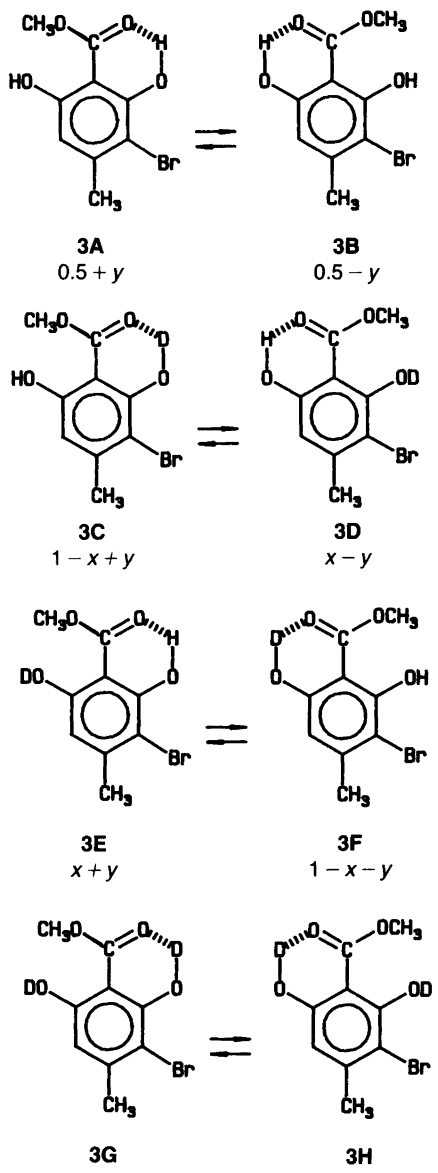


Scheme 2. Isotopomers of **3**.

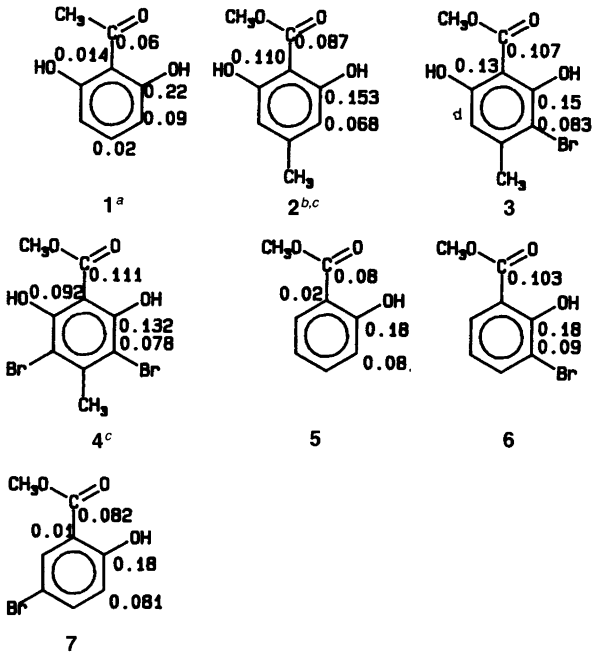
Dhami and Stothers,[9] and these assignments are also valid in $CDCl_3$ as judged from resonance intensities and substituent effects. Deuteriation is achieved by dissolving the compounds in appropriate CH_3OD/CH_3OH mixtures. The degree of deuterium incorporation is varied in order to assign all the observed resonances to the correct isotopomer. As the OH protons and deuterons are labile (exchanging slowly on the NMR time scale, but fast enough to equilibrate during preparation) it is impossible to prepare one specific isotopomer. The deuteriated compounds will always consist of a mixture of isotopomers according to the H:D ratio. A compound with an H:D mixture of 1:1 is called monodeuteriated. In compounds with more than one OH group, partitioning[10] may also take place.

The fact that one cannot isolate the single isotopomers does of course not prevent one from identifying the resonances belonging to the fully deuteriated, the DD isotopomer, the two HD isotopomers or the HH species. The notation DD, HD and HH isotopomers will be used throughout this paper.

The ^{13}C spectra of the symmetrical dihydroxy derivatives **1**, **2** and **4** in $CDCl_3$ are similar. The ^{13}C spectra of the monodeuteriated mixture show several interesting features. Carbons C-2 and C-6 give rise to four rather than to three resonances.[4] Three resonances, one for each isotopomer, were expected. Of the four resonances two are almost equally intense. The center of these two resonances is at the center of the two others, indicating that the monodeuteriated species give rise to two rather than to one signal. This feature is caused by isotopic perturbation of equilibrium (see Discussion).[4] The assignment of the resonances belonging to the DD, HD and HH isotopomers is fully established by varying the H:D ratio. The resonance of the carbon *ipso* to the deuteriated hydroxy group can be identified by means of line-broadening. This feature is clearly observed in the DD isotopomer, and also for one of the resonances belonging to the HD isotopomer. Deuteriation of the hydroxy group also leads to a longer relaxation time for the nearest carbon atoms. This feature becomes even more pronounced if the position *ortho* to the hydroxy group is substituted, as in **3** and **4**. This increase in the relaxation time leads to a decrease in signal intensities under the acquisition conditions used.

The resonances originating from C-3 and C-5 carbons number also four rather than three,[4] whereas C-1 and the carbonyl carbon give three resonances.

The assignment of the ^{13}C resonances of **3** and **4** is greatly helped by a comparison with ^{13}C data of **5**–**7**. Data for these compounds are also given in Table 1. The main feature is that a bromine *ortho* to an hydroxy group leads to a high field



Scheme 3. Deuterium isotope effects in dideuteriated species. Effects for the monodeuteriated species are given in the footnotes. For a discussion of additivity, see text. Footnotes: [a]Values taken from Ref. 4. [b]Isotope effects depend slightly on dilution. [c]Isotope effects in monodeuteriated compounds. **2**: 0.0421(CO), 0.055(C-1); **4**: 0.053(CO), 0.048(C-1). [d]Not resolved.

(low frequency) shift of the *ortho* carbons contrary to substituent effects in simple aromatic compounds.[11]

The splittings caused by isotopic perturbation of equilibrium, called SIP, are given in Table 1. They are fairly similar for one type of carbon within the series **2–4**. The signals originating from C-5 of **3** show, in addition to the four lines ob-

Table 1. ^{13}C and ^{1}H chemical shifts of **1–7** and splittings caused by isotopic perturbation of equilibrium.

	C-1	C-2	C-6	C-3	C-5	C-4	C=O	Other carbons	OH-2	OH-6
1	110.28	161.30	161.30	108.37	108.37	136.09	205.33	33.41(CH_3)	9.64[c]	9.64[c]
SIP[a]		0.42[b]	0.42[b]	0.285[b]	0.285[b]				0.12	0.12
2	97.41	160.46	160.46	108.82	108.82	148.20	169.73	52.43(OCH_3)	9.58	9.58
SIP		0.235	0.235	0.096	0.096			21.79(CH_3)	0.03[d]	0.03[d]
3	98.30	156.65	158.81	102.97	110.09	147.67	169.21	53.02(OCH_3)	10.45	9.34
SIP	0.009	0.242	0.238	0.111	~0.11		0.035		0.0342	0.0405
4	98.90	155.80	155.80	104.06	104.06	147.07	169.08	25.26(CH_3)	10.26	10.26
SIP		0.250	0.250	0.129	0.129			53.72(OCH_3)	0.0451	0.0451
5	112.26	161.52	129.76	117.43	118.98	135.51	170.41	52.12(OCH_3)	10.74	–
6	113.42	158.08	129.02	111.12	119.71	138.80	170.01	52.62(OCH_3)	11.43	–
7	113.72	160.49	132.05	119.42	110.64	138.24	169.31	52.46(OCH_3)	10.67	–

[a]SIP is the splitting in ppm observed for the HD isotopomers caused by isotopic perturbation of equilibrium. [b]Taken from Ref. 4. [c]Depends slightly on concentration (see Results). [d]Determined at high concentration. Resonance is still broad and some exchange may take place.

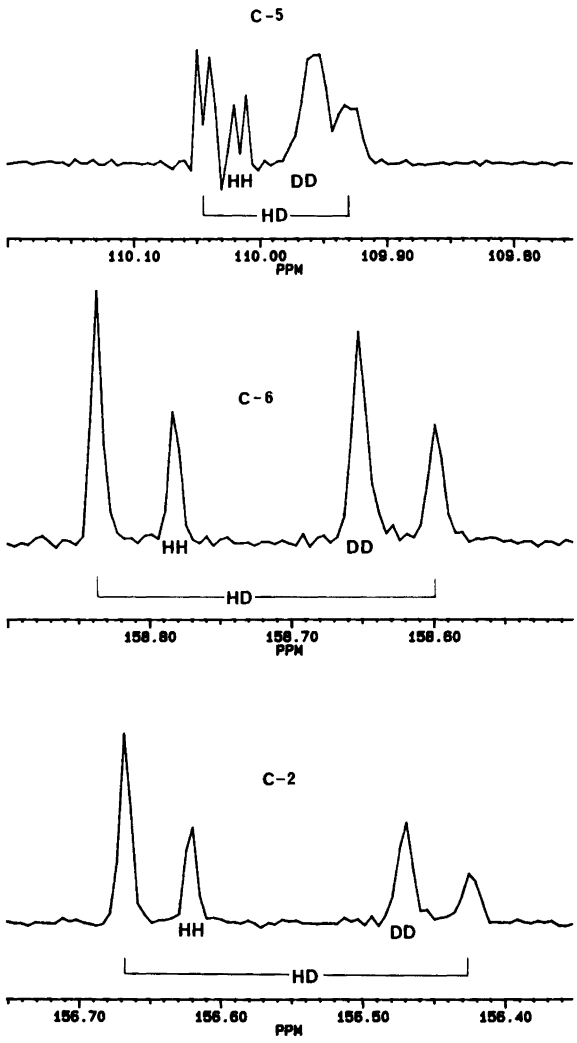


Fig. 1. Resonances originating from C-2, C-6 and C-5 of **3**. Differential line-broadening due to coupling to deuterium is observed for all three carbons. Extra splittings are observed for C-5. All spectra are resolution enhanced.

served in **2**, also extra splittings (Fig. 1). This is as yet unexplained, although it may be tentatively explained on the basis of a long-range effect of the hydroxy group at position 2.

The isotope effects are also given in Scheme 3. $^{n}\Delta C(OD) = \delta C(H) - \delta C(D)$. The $^{2}\Delta C(OD)$ of **5–7** are very similar and slightly larger than those of **2–4** as the latter are averaged values for a free and a hydrogen-bonded case. One interesting feature is the large effect observed at the carbonyl carbon. The effect in the esters is much larger than in the acetophenone. This effect seems also to be sensitive to bromine substitution at position 3, but not very much to substitution at position 5.

The observation of line-broadening due to coupling to deuterium helps clearly to identify the high-field (low frequency) resonance of a SIP pair as being the one close to a deuterium (see Fig. 1). As the rotamer **1B** (see Scheme 1) is less likely than **1A** (*vide infra*) this means that the XC=O group *cis* to a carbon leads to a low-field shift, contrary to the findings in acetophenones and benzaldehydes.[12–14]

^1H NMR spectra. The asymmetry observed in ^{13}C spectra is also reflected in the aromatic region of the ^1H NMR spectrum of **1** (see Fig. 2). In the HH and DD isotopomers the ^1H spectrum of H-3, H-4 and H-5 is of the AA'X type, and with the small AA' coupling (*vide infra*) this turns into a triplet and a doublet for the X and the AA' parts, respectively. For the HD isotopomer the spectrum as shown in Fig. 2 turns into an ABX system. An analysis yields $\delta_{ab} = 3$Hz (at 250 MHz), $J_{ax} = 8.3$ Hz and $J_{ab} = 1.1$ Hz.

Also very significant is the splitting of the OH resonance into two, with a separation of 0.12 ppm for **1** as shown in Fig. 3. The resonance to low field (high frequency) is largest when the deuterium content is high. A high deuterium content corresponds also to a high content of the HD isotopomer compared to the HH species. The relative positions of the two resonances do not move upon dilution, whereas a variation from 9.48 to 9.64 ppm is seen in the resonance position of the OH proton of **1** when the concentration is increased from 2 mg to 12.5 mg per ml. An increase in linewidth from 10.6 to 12.3 Hz is also observed.

The splittings caused by isotopic perturbation at the OH proton of **2–4** are given in Table 1. For **2**, the splitting can only be observed at very high concentrations. A line-broadening, varying from 25 Hz at 1 mg ml^{-1} to 7.4 Hz at 300 mg ml^{-1} is observed, but no change in resonance position is observed on dilution. Both **3** and **4** show much sharper resonances and a much less pronounced dependence on dilution. For **4**, the linewidth is 2.35 Hz at 160 mg ml^{-1} and 3.7 Hz at 1.6 mg ml^{-1}. **3** shows two different SIP's. That of OH-2 is smaller than that of OH-6.

The smaller SIP's observed for **2–4** compared to **1** can be understood since the difference in chemical shift between the free and the hydrogen-bonded state is less in the ester case. This is illustrated by a comparison of the chemical shifts of the OH resonance for 1-methoxymethyl-2-hydroxybenzene (7.07 ppm)[15] and **5**, which are used as references for the free and the hydrogen-bonded states. A difference of 3.7 ppm for the ester compared to 7.6 ppm for **1** is arrived at. Bromination causes a low-field shift of the OH proton of **3** and **4**, but as a similar shift is ob-

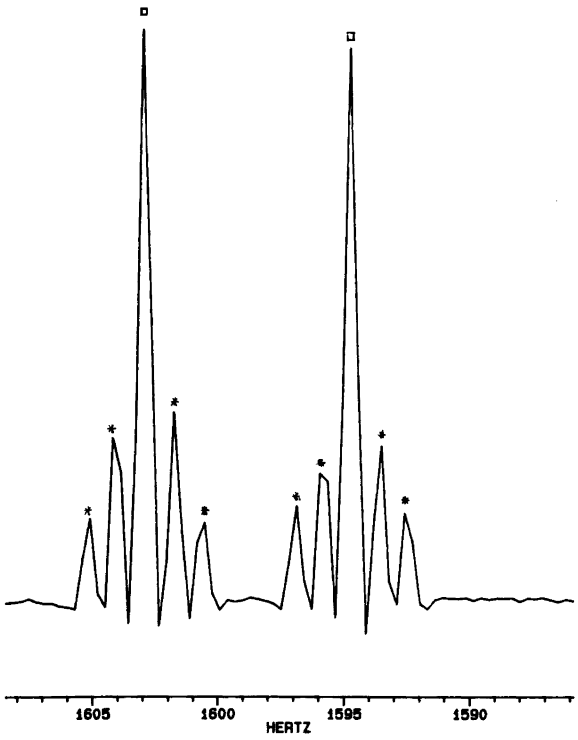


Fig. 2. ^1H spectrum of a deuteriated sample of **1**, showing the resonances of H-3 and H-5. The AA' and AB systems are indicated with squares and asterisks, respectively.

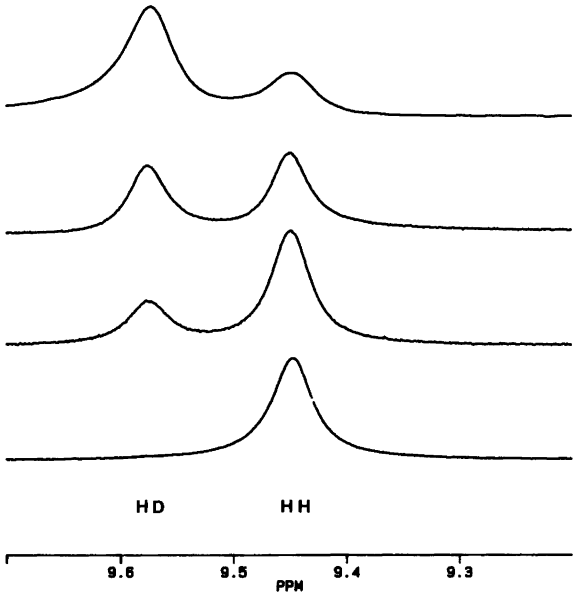


Fig. 3. The OH resonances of a deuteriated sample of **1**. The traces show spectra of compounds with different deuterium content, the upper trace corresponding to the highest deuterium content. The spectra were not recorded at exactly the same concentrations. Resonances of the same type are placed exactly above one another for reasons of clarity.

served for 2-bromophenol compared to phenol, the same difference between free and hydrogen-bonded can be expected for **2–4**.

The ^1H spectra of **2** and **3** show couplings between the CH_3 proton and the H-3, H-5 protons, but no asymmetry of the HD isotopomer of **2** is observed.

Discussion

The main theme of this paper is isotopic perturbation of equilibrium and the information that can be obtained from such an effect. The differences due to isotopic perturbation, called SIP, depend in this case on the difference between the averaged chemical shifts of the carbons and upon the change in the rotamer population.

One interesting and essential point is whether the carbonyl group points preferentially towards the OH or towards the OD group in the HD isotopomers. This can be established unambiguously by looking at the OH resonance. The OH resonances of **1**, **2** and **4** are split into two, that at lower frequency originating from the HH isotopomer and the other from the HD isotopomer. The presence of two resonances rather than one resonance is due to the fact that in the HH isotopomer, one OH group is hydrogen-bonded and the other is free. This resonance thus falls at a position that is the average of that for a hydrogen-bonded (~12–14 ppm) and a non-hydrogen-bonded (~4–7 ppm). The other resonance belongs to the HD species. As the latter is at lower field (higher frequency), the HD isotopomer with the OH group hydrogen-bonded (**1A**, **2A**, **4A**) is more abundant than **1B**, **2B** and **4B** according to the above-mentioned facts. The assignment of the two resonances is confirmed by recording spectra at varying D-content. It is hence proven that an OH···O bond is preferred to an OD···O bond. Buckingham and Fan-Chen[8] have treated the problem of differences in the hydrogen-bond strength of OH and OD bonds, and concluded that no general answer can be given to this question. The reason is that the bending and stretching vibrations of the H- and D-bonds make opposing contributions. The results obtained in the present study are hence supposed to be valid for systems with a similar shape of the potential energy surface. Novak[16] has conducted a series of IR measurements in the solid state and found positive isotope effects when the potential function contains a symmetric or an asymmetric double potential minimum. The positive isotope effect implies a weakening of the hydrogen-bond on deuteriation, a finding completely in line with ours. This study thus shows this to be valid also for intramolecular hydrogen-bonded compounds in solution.

Additivity of ^{13}C chemical shifts has been es-

tablished or assumed in many instances. However, a comparison of the ^{13}C chemical shifts of **5** with those predicted from simple substituent effects shows immediately that the chemical shifts around the functional group are predicted poorly. This has also been observed for e.g. *o*-phthalates, in which the two carboxyl groups interact.[17] The lack of additivity is closely related to the anisotropy of the chemical shift tensor for substituents such as RC=O, ROC=O, etc. This anisotropy is averaged in non-hindered cases, but can in oriented cases give effects quite different from those predicted from results for simple compounds. It is interesting that the observed chemical shift of the C-2 resonance is at a much lower field than that predicted, whereas that of C-6 is at a higher field. The anisotropy of the $CH_3OC=O$ group seem to be quite large, although it has never really been determined.

The anisotropy of the $CH_3C=O$ group can be estimated from a comparison of chemical shifts for 2,4- and 2,6-dihydroxyacetophenone, and a value of 7.6 ppm is arrived at. The signal for the carbon *cis* to the carbonyl group lies at low field. This is the opposite of the findings of Drakenberg *et al.* for both a HC=O and a $CH_3C=O$ group.[12,13] However, further support for our finding is provided by the fact that the resonance at low frequency (high field) of the C-2, C-6 HD SIP pair is attributable to the carbon with a deuteriated hydroxy group. This shows unambiguously that the C=O groups deshields the carbon in a *cis* position rather than shields it as found for aldehydes and acetophenones.[12,13] This finding cannot only be ascribed to a difference in shielding of the XC=O group, but must to a large extent be ascribed to a change in the -OH function upon hydrogen-bonding and a concomitant change in the nuclear shielding of the *ipso* carbon (*ipso* to the OH group). The considerable anisotropy of the $CH_3C=O$ and $CH_3OC=O$ groups is thus probably caused by the interaction with the OH group itself.

The appearance of four rather than three resonances for C-2 and C-6 of **1**, **2** and **4** can thus be explained by the finding that one rotamer of the HD species is more highly populated than the other and that the XC=O group is highly anisotropic. The anisotropy is not supposed to extend to the C-3 and C-5 carbons.[12] The four rather than three resonances observed for C-3 and C-5 of **1**, **2** and **4** are explained by recognizing that if the XC=O group points preferentially towards the OH moiety, then the OH hydrogen also points preferentially towards the C=O group. As the OH group is also anisotropic, this will likewise cause an extra splitting of the resonances for C-3 and C-5 in the HD isotopomer. The fact that the OH group points preferentially in one direction is also seen in the ^1H spectrum. The aromatic part of **1** gives rise to an ABX spectrum for the H-3, H-4 and H-5 protons of the HD isotopomer (see Fig. 2).

The anisotropy of the -OH group is thus clearly demonstrated, a fact that is particularly important when trying to predict ^{13}C chemical shifts for compounds with intramolecularly hydrogen-bonded OH groups.

The splittings caused by isotopic perturbation of equilibrium can be used to calculate the difference in rotamer population if the difference between the chemical shifts of the equilibrating nuclei are known in the static cases. As the values for the static cases must be derived using model compounds, this approach will lead only to approximate values, but still to trends that can be quite useful.

Knowing the rotamer distribution, energy differences can also be predicted. A preliminary account for **1** has been given in Ref. 4 using a very approximate chemical shift difference. Using the shift difference of 7.6 ppm described above, SIP(C-2, C-6) yields a rotamer ratio of 52.8:47.2, whereas the ^1H data yield a ratio of 51.8:48.2. These ratios are equivalent to energy differences of 0.28 kJ mol^{-1} and 0.18 kJ mol^{-1}, respectively. These values are quite different from that given in Ref. 4, which was wrong. The energy difference is quite similar to those obtained for a number of carbonium ions.[3] This similarity is understandable, as the C-H and the O-H stretching frequencies, which are the energetically dominant vibrations, are similar.

Both the ^1H and the ^{13}C NMR spectra of deuteriated **3** are unique in the number of equilibrium isotope effects observed and are hence suitable objects for a total analysis. OH proton resonances as well as C=O, C-1, C-2, C-3, C-5 and C-6 carbon resonances show splittings due to isotopic perturbation. The rotamer population due to this is called x, as shown in Scheme 2. The rotamer populations can in principle also be per-

turbed as a result of the presence of the bromine substituent. This deviation is called y, as also seen in Scheme 2.

The SIP's for **3** can be calculated in the following fashion, illustrated for the carbonyl carbon. The average chemical shift for the carbonyl carbon of the structures **3C** and **3D** is given by

$$\delta CO_{C,D} = (1-x+y)\delta CO_{cis} + (x-y)\delta CO_{trans}$$

and the average shift for **3E** and **3F** by

$$\delta CO_{E,F} = (x+y)\delta CO_{cis} + (1-x-y)\delta CO_{trans}$$

The SIP(CO) is the difference between $\delta CO_{C,D}$ and $\delta CO_{E,F}$, leading to eqn. (1). Eqns. (2)–(5) are arrived at similarly. Δ has not been taken into account in these equations, which can be adapted to the symmetrical case by removing y. δOH_{HB} denotes the chemical shift of the hydrogen-bonded OH proton.

$$SIP(CO) = (\delta CO_{trans} - \delta CO_{cis})\,(1-2x+2y) \quad (1)$$

$$SIP(C\text{-}1) = (\delta C\text{-}1_{trans} - \delta C\text{-}1_{cis})\,(1-2x+2y) \quad (2)$$

$$SIP(C\text{-}2, C\text{-}6) = (\delta C\text{-}2_{trans} - \delta C\text{-}2_{cis})\,(1-2x) \quad (3)$$

$$SIP(OH\text{-}2) = (\delta OH - \delta OH_{HB})\,(0.5-x-y) \quad (4)$$

$$SIP(OH\text{-}6) = (\delta OH - \delta OH_{HB})\,(0.5-x+y) \quad (5)$$

The chemical shift difference for the carbonyl carbon in the two rotamers (**3C** and **3D**) can be estimated from data for **6** and **7** to be equal to 0.7 ppm (see Table 1). As the SIP value is 0.035 ppm, eqn. (1) leads to an $x-y$ value of 0.524. C-1 is treated similarly. The shift difference between the C-1 resonances for **A** and **B** can likewise be estimated to be 0.3 ppm, and as the SIP value is 0.009 ppm we arrive at an $x-y$ value of 0.515. This value must be used with some care as it is obtained by division of two very small numbers. From the ^{1}H NMR spectrum of **3** we obtain two SIP's for the two OH protons, as seen in Table 1. x and y can hence be determined by means of eqns. (4) and (5) if the difference in chemical shift between the free and the hydrogen-bonded protons can be estimated from data for model compounds. A difference of 3.7 ppm is estimated (see Results). Eqns. (4) and (5) give x and y as 0.510 and −0.001, respectively. This shows that the bromine does not influence the rotamer distribution to any large extent. The change in the distribution can be caused in three ways: directly as a dipole-dipole interaction, indirectly because the bromine render one of the OH groups a better hydrogen-bond-former, or because the bromine forms a weak hydrogen-bond with the OH group, which in turn is less strongly hydrogen-bonded to the carbonyl group. Intuitively one expects the bromine to render the *ortho* hydroxy group a better hydrogen-bond maker because of the inductive electron attraction. However, the following facts must be explained. $^2\Delta$ is slightly larger for C-2 than for C-6 in **3**, and $^2\Delta$ for C-6 is smaller than that observed for **2**; furthermore, the rotamer **3B** is preferred to **3A**.

If we assume that the magnitude of $^2\Delta$ reflects the strength of the hydrogen-bond, then the hydrogen-bonds of **3** are weaker than or equal in strength to those in **2**. This is not consistent with a model in which the bromine leads to stronger hydrogen-bonds or a model in which the bromine weakens the hydrogen-bond of the hydroxy group at C-2. The most likely cause is hence a repulsion between the bromine and the $COOCH_3$ group.

In *m*-substituted benzaldehydes, the O-*cis* rotamer is the most highly populated (O-*cis*:O-*trans* = 0.59:0.41 for 3-bromobenzaldehyde).[12] Drakenberg *et al.*[12] suggest two explanations. Either H-2 becomes more positive due to the bromine or dipole-dipole repulsion destabilizes the O-*trans* rotamer. The latter seems the most probable. That the esters show a rotamer ratio much closer to unity than ketones is also demonstrated in α,β-unsaturated esters.[18] Our results show that the opposite rotamer to that found in aldehydes is

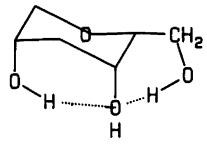


Fig. 4. One possible situation in which deuterium perturbation of equilibrium can occur in carbohydrates. Only the relevant part of the molecule is shown. The oxygen of the OH-4 group is considered as the hydrogen-bond acceptor. If the orientation of the lone-pairs of OH-4 reorient according to hydrogen-bonding to OH-2 or to CH_2OH then a situation similar to that found in **3** exists.

preferred for **3**, and that this most likely is caused by dipole-dipole repulsion between the bromine and the OCH_3 group of **3A**. That the aldehydes and the esters should behave oppositely is supported by studies of ^2J(CO,C) coupling constants for esters and ketones.[19]

The rotamer populations for **3** obtained by the different SIP's are $x = 0.51$, 0.524 and 0.515. For **4**, a similar rotamer population (0.518) is found using SIP(OH-2). This value is again very similar to that obtained for **1**. Using a rotamer distribution of 0.513 a shift difference between C-2 and C-6 of 10 ppm is obtained for **3** and **4**. This value is most likely also valid for **2**. Furthermore, this rotamer distribution leads to an energy difference between the **A** and **B** rotamers of 0.15 kJ mol^{-1}, an energy difference in the same range as found for **1**.

The observation of SIP's for the carbonyl carbon and for C-1 of **3**, as well as the extra splitting at C-5, show clearly that isotopic perturbation of equilibrium can be extensive in non-symmetrical systems. A similar although not identical case has been studied in carbohydrates. The SIMPLE[20,21] technique has proven effective in these systems, but has also led to some controversy. The occurrence of extra splittings has been interpreted in two different ways for carbohydrates.[20,21] The present study shows clearly that effects may be relayed to carbons quite far from the center of deuteriation. This also occurs frequently in carbohydrates (Fig. 4). These examples illustrate clearly that caution should be exercised in systems in which multiple isotopic perturbation of equilibrium may occur, such as carbohydrates.

Conclusions

The isotopic perturbation of equilibrium effects observed in these compounds are interesting for several reasons. They have helped to prove that an OH group forms a stronger hydrogen-bond than an OD group. Secondly, they lead to an estimate of the anisotropy of XC=O groups involved in hydrogen-bonding. Most importantly, they illustrate the multitude of effects (splittings) that can occur.

The non-equivalence of H-3 and H-5 of the HD isotopomer of **1** is an example of what is termed a relay effect, as it is caused by deuteriation of the hydroxy group which in turn causes the C=O group to point preferentially towards the OH group. This causes the OH hydrogen to point preferentially in one direction, which in the end leads to different chemical shifts for H-3 and H-5. Furthermore, the effects at C=O and C-1 of the non-symmetrical **3** are also an indication of the subtle effects that may be observed.

Experimental

Compounds **1**, **2** and **5** are commercial products (Aldrich Chemie, Weinheim, Germany). **3**, **4**, **6** and **7** are prepared by bromination of **2** and **5**, respectively, in $CHCl_3$ with equivalent amounts of bromine. **2** was brominated at room temperature, whereas **5** was brominated under reflux conditions. No attempts were made to separate the isomers.

NMR experiments. The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker AC250 spectrometer operating at 250 and 62.9 MHz, respectively. The digital resolution for ^1H spectra was 0.6 Hz per point and for ^{13}C spectra 0.24 Hz per point. The chemical shifts are quoted relative to TMS. The temperature was 300 K. Concentrations were varied in order to eliminate concentration effects and the deuterium content was likewise varied.

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