Intrinsic deuterium isotope effects on NMR chemical shifts of hydrogen bonded systems

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Abstract This mini review describes intrinsic deuterium isotope effects on ^{13}C chemical shifts of rigid hydrogen bonded compounds primarily in solution. The steric effects of intramolecularly hydrogen bonded compounds are dissected into different bond interactions leading either to steric compression or to steric twist. One-bond isotope effects involving CH(D) bonds are analyzed in terms of substituent effects and the question is raised whether isotope effects can be useful in the study of CH-hydrogen bonds.

Key words CH-hydrogen bonds • deuterium isotope effects • intramolecular hydrogen bonds • intrinsic isotope effects • nuclear shielding • steric effects

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The present mini review will deal with deuterium isotope effects on chemical shift of hydrogen bonded compounds in solution. For recent more complete reviews see [7, 8, 25] and for isotope effects primarily on intermolecular hydrogen bonding and in the solid state the papers by the Limbach group [3, 4, 33, 34]. The paper will concentrate on intrinsic isotope effects and not so much on equilibrium ones. The review will also concentrate on situations with rigid molecules. Deuterium isotope effects on chemical shifts are easily measured provided the deuterium is not exchanging at the NMR time scale. An example is given in Fig. 1. The main reason for obtaining a different chemical shift in the isotope substituted compounds can clearly be related to the shape of the potential well and the different zero point energy of XH and XD bonds (see Fig. 2). A prerequisite for obtaining an isotope effect is an asymmetric potential. The isotope effect on chemical shifts is a ground state property. For many of the situations encountered only the zero point energy level is appreciably populated. However, if other levels are populated then the effect will also take into account the different populations of the protio and the deuterio species [15].

The asymmetry of the potential plays a major role. For XH bonds, X being an electronegative element such as oxygen, nitrogen or sulphur, hydrogen bonding is very important. In general, any feature that influences the bond order of the XD bond in question is important.

If we accept the theory of Jameson [26], we get the isotope effect expressed as the nuclear shielding difference:

$$<\sigma> - <\sigma^*> = \delta\sigma/\delta r_1 [<\Delta r_1> - <\Delta r_1>^*] + \text{other smaller terms}$$

This is valid for both one-bond and long range isotope effects. Obviously, in the latter case, substitution may

influence not only the XH bond but also the transmission of effects over several bonds as demonstrated in *o*-hydroxyacyl benzenes [2, 14, 17, 18, 23, 38]. These studies showed that electron donating substituents ortho or para to the acyl group leads to a stronger hydrogen bond and generally numerically larger isotope effect on carbon chemical shifts (see discussion of $^4\Delta C=O(OH)$ later). An example is given in Scheme 1 comparing with *o*-hydroxyacetophenone. Electron withdrawing substituents like acetyl, nitro, nitrilo etc. ortho or para to the hydroxy group has the same effects. For systems containing more than one hydrogen bond unit (RC=O...H-O) (see Scheme 1C) a synergy is obtained if the systems are next to each other thereby creating bond fixation of the benzene ring [2]. However, hydrogen bonding can only be strengthened to a certain extent by electronic factors. To obtain even stronger hydrogen bonds and numerically larger isotope effects steric effects must be introduced. Steric effects can be of two types as seen in Scheme 2, either involving six or seven atoms (e.g. H-C-C(=O)-C_1—C_1-O in the former case). In the former case one obtains steric compression and in the latter case steric twist [38]. Steric compression may lead to rather strong hydrogen bonds.

Steric compression effects can also be seen in Schiff bases depending on the size of R' (Scheme 3A) [9]. Also R plays a role as demonstrated in Scheme 3B. In case of 3B the steric compression leads to stronger hydrogen bonds that results in a tautomeric situation clearly reflected in the very large isotope effects at most positions. For a series of *o*-hydroxyacyl aromatics (salicylaldehyde, *o*-hydroxyacetophenone (Scheme 1A) and 1,3,5-triacetyl-2,4,6-trihydroxyacetophenone (Scheme 1C) and similar compounds) isotope effects have
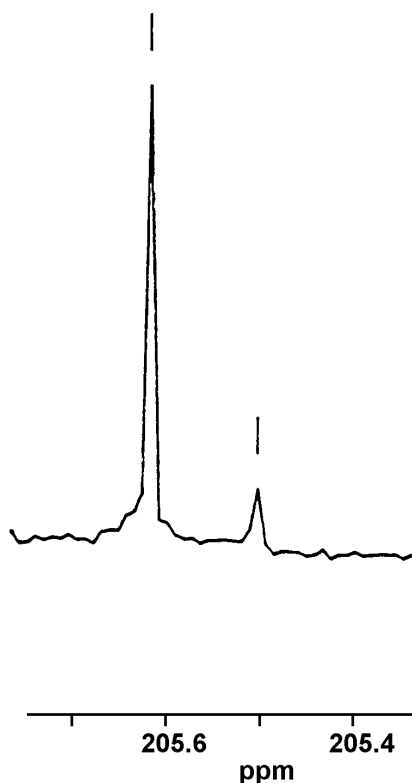
been calculated using *ab initio* methods [1, 2]. The changes in ^{13}C chemical shifts as a result of OH bond changes upon deuteriation turned out to be rather similar for different compounds, whereas the change in the mean OH distance upon deuteriation changed very strongly with the hydrogen bond strength and the O-H bond length (R_{OH}). $^2\Delta C(OH)$ could be correlated with $R_{O...O}$, R_{OH} and $R_{O...H}$ [2].

For the interaction paths involving six-atoms (Scheme 2B) a twist is observed. Examples are 1-acetyl-2-hydroxynaphthalene and similar compounds [20]. Recent theoretical calculations have shed more light on this type of isotope effect. The C-1-C=O bond is squeezed out of the naphthalene ring plane, whereas the C=O bond points towards the O-H bond, which is in the ring plane [38]. A rather simple method to distinguish between steric compression and steric twist is to measure the isotope effect at the OH chemical shift, when the $CH_3C=O$ group is deuteriated (this is easily achieved in most cases by prolonged treatment with CH_3OD). For the steric compression cases no, or only very small, isotope effects are observed, whereas in the steric twist case rather large isotope effects are observed [20].

A combined effect of steric compression and steric twist is found in N-phenyl enaminones with substituents either at C-α or at the C-2', C-6' [39].

A question that is intimately related to hydrogen bonding is: can the isotope effects be transmitted via the hydrogen bond? Early studies clearly indicated this as isotope effects are seen at the carbonyl carbon of Z-enaminones, whereas no effects were seen at the carbonyl carbon of E-species [16]. Furthermore, for purpurogallins long range isotope effects were seen indicating that these were transmitted via the hydrogen bond [18].

As seen from Scheme 4 four bond isotope effects of the type $^4\Delta C=O(OH)$ can be rather large. The increase from *o*-hydroxyacetophenone is obvious. On the other hand, the 2-hydroxy-3,6-dimethoxyacetophenone (Scheme 1B) shows a small $^4\Delta C=O(OH)$, a trend that has been confirmed for a series of compounds. The clearcut difference between these compounds can be illustrated in the form of the resonance structures in Scheme 5. The A form enhances the isotope effect at the carbonyl carbon, most likely via the hydrogen bond.
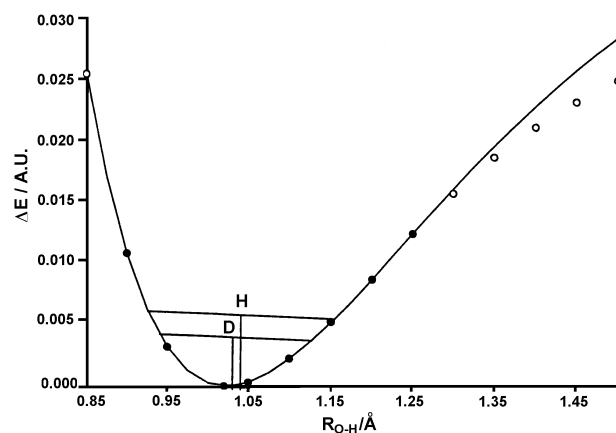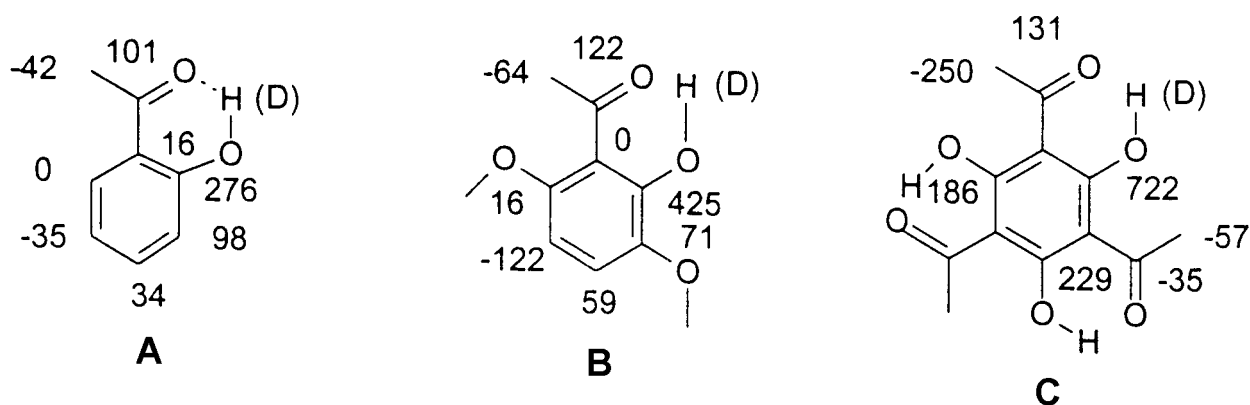

Fig. 1. Exert of a ^{13}C NMR spectrum showing the carbonyl carbon region of 2-hydroxy-3,6-dimethoxyacetophenone partially deuteriated at the OH group (Scheme 1B). The smaller resonance belongs to the deuteriated molecule.

Fig. 2. Potential energy curve of a hydrogen bonded *o*-hydroxyacyl benzene.

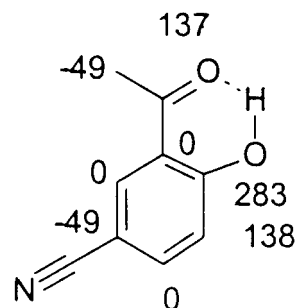**Scheme 1.** Deuterium isotope effects on ^{13}C chemical shifts. Data for A [18] and C [2] (in ppb).
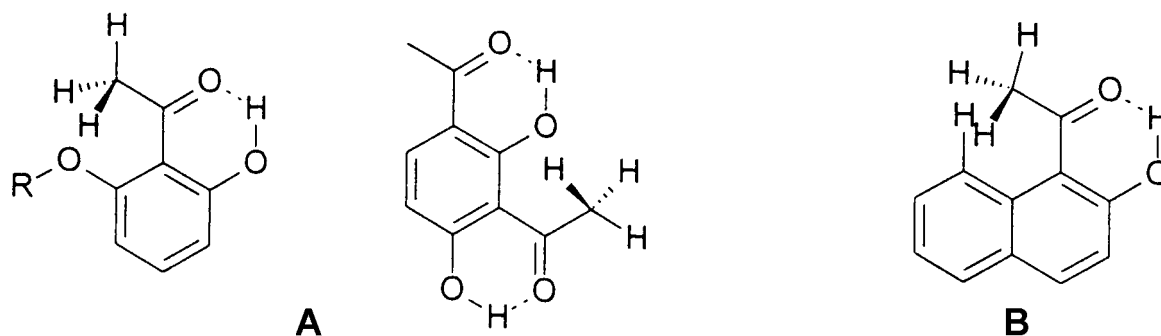
Scheme 2. Illustration of interactions. In A six atoms are involved in the interaction (typically H-C-C_{CO}-C_{ar}-C_{ar}-O). In B seven atoms are involved (H-C-C_{CO}-C_{ar}-C_{ar}-C_{ar}-H).


Scheme 3. Deuterium isotope effects on ^{13}C chemical shifts of Schiff bases (in ppb). Data for A from Rozwadowski [32]. Data for B strongly temperature dependent. Recorded at 250 K in CD$_2$Cl$_2$.

So far only ^{13}C and to a small extent ^{1}H have been treated. Obviously, for systems like the ones shown in Schemes 1, 2B and 3 isotope effect at oxygen could be considered and for Schiff bases (Scheme 3) isotope effects at ^{15}N chemical shifts are most useful [24]. Many Schiff bases are tautomeric. This has a profound effect on the isotope effects [8, 24]. For those not tautomeric a $^{5}\Delta$N(OH) isotope effect of ~1.0 ppm has been observed [24].

In case of oxygen this is more difficult as the only observable oxygen nucleus, ^{17}O, is a quadrupolar nuclei giving rather broad resonances. Isotope effects at both the OH and C=O oxygens can be observed in e.g. salicylaldehyde, 2-hydroxy-1-acenaphthone (Scheme 2B) and others [6, 28]. The effect are found to be proportional to the hydrogen bond strength [6].

Scheme 4. Two- and four bond deuterium isotope effects on ^{13}C chemical shifts of substituted *o*-hydroxyacyl benzenes (in ppb). Electron withdrawing substituent.
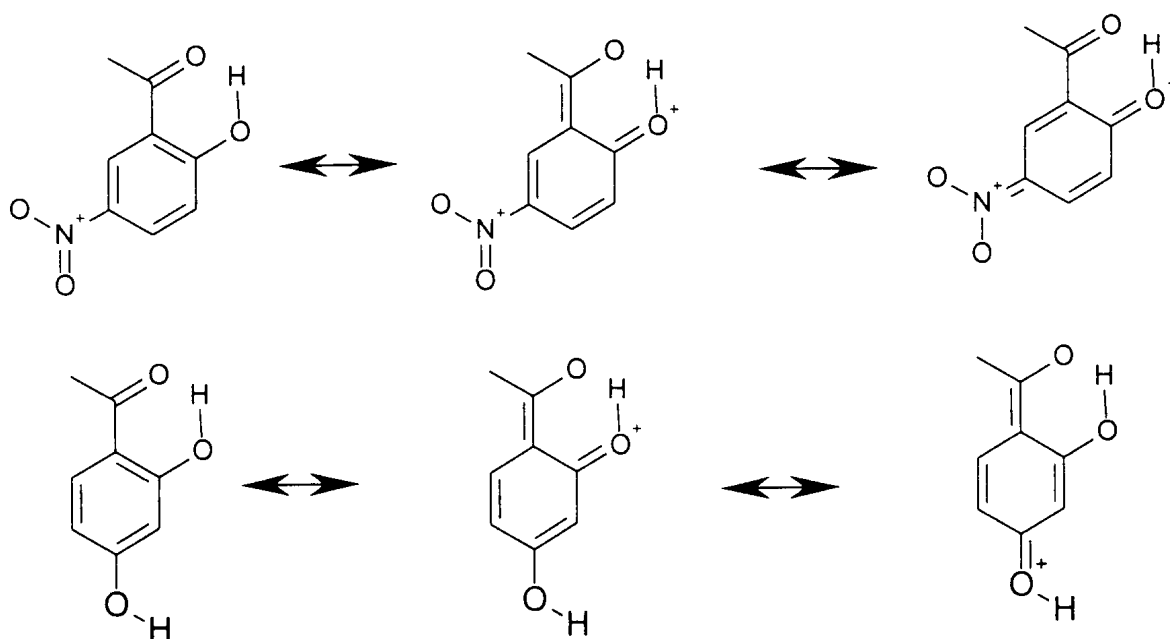
Scheme 5. Resonance structures of nitro and hydroxy derivatives of *o*-hydroxyacyl benzenes.
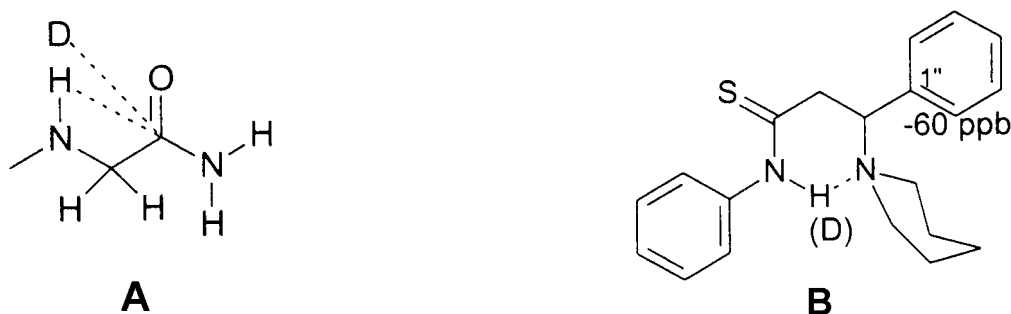
Scheme 6. Electric field effects in deuteriated protines (A) [37] and thioamides (B) (only the long range effect is shown).

The compounds treated so far have been of the RAHB (resonance assisted hydrogen bonding) type [5, 11, 12, 16]. The acceptor is electronically coupled to the donor by a double type bond. If this is not the case as in proteins (Scheme 6A) or in the thioamides (Scheme 6B) a different type of isotope effect may be observed [21, 37]. To observe an isotope effect at C-1" of Scheme 6B is rather unusual (many other similar long range effects are seen in systems in which C-2 and C-3 are part of five- or six-membered rings) [35] as deuterium isotope effects at e.g. carbon chemical shifts in aliphatic systems are only transmitted over 3–4 bonds. These long range effects are ascribed to electric field effects caused by the strongly polarised NH(D) bond. The isotope effects are caused, as originally suggested by Gutowsky [13] by the difference in the average bond length of the NH and ND bonds. This kind of effect clearly depends on a large charge at NH. This will typically be found in hydrogen bonded thioamides but also in hydrogen bonded amides (proteins) [37]. This kind of effect can be expected in other systems with polarized bonds. One such example could possibly be carbohydrates, in which many unusual long range isotope effects are observed.

Long range effects are best studied using chemical shift sensitive nuclei such as ^{13}C, ^{14}N and ^{19}F. Investigations of ^{19}F chemical shifts have turned out to give good insight into the mechanism of long range isotope effects [10, 22].

CH bonds

Isotope effects involving CH(D) bonds have typically been concentrated on effects caused by hybridization and bond order. One bond isotope effects have been studied in acetylderivatives. Some variation is seen between ketones, esters and lactones [15].

Recently, LeMaster *et al.* [27] have found that $^{1}\Delta C(D)$ for glycines of proteins depended on the back bone conformation again showing the importance of conjugation to the CONH group and the interaction with the NHC=O group. The CO conjugation was also found in a model system, norcamphor [30].

Can one-bond $^{1}\Delta C(D)$ isotope effects be used to study CH-hydrogen bonding (we find it of paramount importance to use the term CH-hydrogen bonding to distinguish this kind of interaction from normal hydrogen bonds)? This type of hydrogen bonding has been debated very much recently [29, 36]. The CH-hydrogen bond is supposed to lead to a shorter CH bond [29]. Deuterium substitution should therefore lead to a smaller isotope effect than in similar compounds without hydrogen bonding if we can make a conclusion parallel to that obtained for OH (see above). We find some of the present compounds suitable in studies of such compounds as

the distances are short (Scheme 2A). Furthermore, in the study of methyl groups with all degrees of deuteration a possible non-additivity may appear if the interactions are strong [15]. We have done a study of one bond deuterium isotope effects of the methyl groups of some of the compounds like 1,3-diacetyl-2,4-dihydroxy-6-methoxybenzene, 1-acetyl-2-hydroxy-6-methoxybenzene and 1,3,5-triacetyl-2,4,6-trihydroxybenzene deuteriated at the acetyl group and compared the data with acetophenone [15]. 1,3-diacetyl-2,4-dihydroxy-6-methoxybenzene and 1,3,5-triacetyl-2,4,6-trihy-droxybenzene (see Scheme 1C) belong to the group of sterically compressed compounds and judging from the two-bond deuterium isotope effects [38] the hydrogen bonds are strong. This is partly a consequence of steric compression as the distance between the oxygen and the methyl hydrogens is small; a good position for a putative CH-hydrogen bond. The study shows that for acetophenone the effects is 0.244 ppm/D [15], whereas for 1-acetyl-2-hydroxy-6-methoxyben-zene it is 0.245 ppm. Values of 0.242 and 0.240 ppm are found for the acetyl groups of 1,3-diacetyl-2,4-dihydroxy-6-methoxybenzene and 0.242 ppm for and 1,3,5-triacetyl-2,4,6-trihydroxybenzene. No clearcut effect related to CH-hydro-gen bonding has thus been observed. The situation is akin to that of solvated deuteriated ammonium ions [19, 31] in which the isotope effect is mainly ascribed to an electric field effect. The effect is maximal for a directional position of the water (oxygen) and close to zero for a non-directional hydrogen bond [19, 31]. The latter situation is alike the situation seen in the present compounds and possibly explaining the absence of an effect.

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