MAGNETIC RESONANCE IN CHEMISTRY, VOL. 32, 399–408 (1994)

Deuterium and ^{18}O Isotope Effects on ^{13}C Chemical Shifts of Sterically Hindered and/or Intramolecularly Hydrogen-Bonded *o*-Hydroxy Acyl Aromatics

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A series of sterically hindered *o*-hydroxy aromatic ketones were synthesized, including benzene, naphthalene, phenanthrene and pyrene derivatives. Deuterium isotope effects on the ^{13}C chemical shifts of 2-hydroxy-1-acenaphthone and other sterically hindered, intramolcularly hydrogen-bonded aromatic ketones (OH exchanged) are shown to be unusual. The two-bond isotope effects are very large. Likewise are the istope effects on C=O, C—1, C—3 and C—4 carbon resonances and some show unusual signs. These unusual effects are explained by a higher degree of twist in the deuterio than the protio compound. Steric isotope effects are also observed on OH chemical shifts of sterically hindered *o*-hydroxy acetyl aromatic compounds deuteriated at the methyl group. These isotope effects show non-additivity. For one-bond isotope effects, $^1\Delta^{13}C(^{18}O)$, hydrogen bonding leads to a decrease, whereas twisting of the carbonyl group leads to an increase. Two hydrogen bonds to the same acceptor has a reduced cumulative effect. Data for sterically hindered, hydrogen-bonded compounds are found to fall outside the correlation between $\delta(^{17}O)$ and $^1\Delta^{13}C(^{18}O)$.

KEY WORDS NMR NMR Isotope effects on ^{13}C chemical shifts Deuterium isotope effects ^{18}O isotope effects Intramolecular hydrogen bonding Steric strain Hydrogen bond strength

INTRODUCTION

Proton chemical shifts[1,2] of OH groups and two-bond deuterium isotope effects on ^{13}C chemical shifts[3–12] have been used extensively to describe intramolecular hydrogen bonds [deuterium isotope effects on chemical shifts are defined as $^n\Delta X(OD) = \delta X(H) - \delta X(D)$, where X in this study is either ^1H or ^{13}C; ^{18}O isotope effects are defined similarly]. Plots of δ(OH) *vs.* $^n\Delta C(OD)$ may be used to characterize hydrogen-bonded systems.[4–6,8–10] Data for 2-hydroxy-1-acenaphthone[8] revealed that the isotope effects in this compound are different from those for similar *o*-hydroxy acyl aromatics.[4,6–10] This paper presents data for a series of *o*-hydroxy aromatic ketones synthesized to give various degrees of steric strain and strength of the hydrogen bonds. Fluorine was incorporated to monitor this phenomenon by means of through-space carbon–fluorine coupling constants.

One-bond ^{18}O isotope effects on ^{13}C chemical shifts, $^1\Delta^{13}C(^{18}O)$, have been correlated with C=O chemical shifts for a broad range of compounds.[13] Addition of data for intramolecular hydrogen-bonded compounds showed that these fall on separate lines depending on the number of hydrogen bonds.[14] Furthermore, acid fluorides fall off the predicted line.[15] ^{13}C NMR data for sterically hindered, intramolecularly hydrogen-bonded carbonyl compounds are not well represented in the literature.

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$^1\Delta^{13}C(^{18}O)$ isotope effects have been extensively characterized,[16–18] and this type of parameter is useful in the description of acetophenones. $^1\Delta^{13}C(^{18}O)$ isotope effects correlated well with Hammett σ_p^+, *ipso* carbon chemical shifts and other parameters.[16] Recently, $^1\Delta^{13}C(^{18}O)$ isotope effects have been correlated with ^{17}O chemical shifts.[18] Clearly, such a relationship makes both parameters more versatile.

o-Hydroxy acyl compounds have not been subjected to structure investigations, except for a few x-ray structures of acetophenones[19,20] and benzophenones.[21–23] These structures are not easily described by conventional NMR parameters.

This work was aimed at using a multiple parameter approach, including O*H* and ^{13}C chemical shifts, deuterium and ^{18}O isotope effects on ^{13}C chemical shifts, carbon–fluorine and hydrogen–fluorine through-space couplings when appropriate and temperature dependence, to describe the hydrogen bonds and structures of intramolecular hydrogen-bonded compounds, in which the carbonyl group is subject to steric hindrance.

ASSIGNMENTS

Chemical shifts and assignments for unpublished compounds are given in Table 1. The assignments and chemical shifts of some of the compounds have been given previously, **1**,[8] **2**,[24] **7**,[25] **8**,[25] **9**[25] and **10**.[25] The assignment of **6** was greatly helped by the observation

CCC 0749–1581/94/070399–10

Received 16 November 1993
Accepted (revised) 26 February 1994

Table 1. ^{13}C chemical shifts (in ppm) of *o*-hydroxy acyl aromatics

Compound	C-1	C-2	C-3	C-4	C-4a	C-4b	C-5	C-6	C-7	C-8
3	118.2	163.2	118.8	136.2	—	—	118.8	129.9	210.6	35.0
4	112.8	163.3	111.6	161.8	—	—	107.2	128.9	205.2	39.7
5	117.5	163.6	119.3	135.3	—	—	117.8	130.9	212.2	44.6
6	111.7[a]	160.0[a]	112.8	132.6	—	—	105.8	158.8	212.0	44.5
11	115.0	163.0	119.6	136.7	128.5	—	124.3	123.5	127.8	129.3
12	114.4	160.1	118.4	135.1	127.7	—	123.3	122.8	126.8	128.2
13	115.4	162.5	119.6	136.6	128.5	—	124.3	123.6	127.8	129.3
14[b]	n.m.[c]	164.2	118.5	139.7	n.m.	—	125.0	128.4	128.7	124.1
15	114.4	161.1	119.0	136.0	128.3	—	126.1	123.6	126.6	129.3
16	n.m.	159.7	113.8	n.m.	—	—	n.m.	n.m.	n.m.	n.m.
17	121.4	126.1	130.0	124.4	133.1	128.8	122.3	123.5	126.2	124.4
18	121.6	126.7	130.6	124.7	133.1	n.m.	123.0	131.8	125.3	124.3
19	n.m.	156.6	106.4	130.0	—	—	107.9	158.0	209.4	44.9
20	162.9	115.5	136.2	118.7	141.9	—	—	—	—	—

	C-8a	C-9	C-9a	C-10	C-10a	C-11	C-12	C-13	C-14
3	—	19.3	—	—	—	—	—	—	—
4	—	13.9	—	7.4	—	18.6	—	—	—
5	—	28.7	—	—	—	—	—	—	—
6	—	25.8	—	—	—	—	—	—	—
11	131.5	208.2	—	37.2	—	9.5	—	—	—
12	130.6	212.1	—	38.6	—	18.8	—	—	—
13	131.5	207.8	—	45.7	—	18.9	13.7	—	—
14[b]	n.m.	185.4	—	116.3	—	—	—	—	—
15	132.2	200.2	—	140.1	—	128.4	128.3	132.5	—
16	n.m.	n.m.	—	n.m.	n.m.	206.6	33.8	—	—
17	125.2	110.9	—	161.9	124.5	202.9	30.7	—	—
18	132.4	110.7	—	163.8	n.m.	202.9	30.8	196.5	25.6
19	—	26.3	—	—	—	—	—	—	—
20	—	194.0	115.8	32.8	—	—	—	—	—

[a] Measured at 220 K.
[b] Measured at 220 K.
[c] Not measured.

of carbon–fluorine coupling constants. The assignment of **3–5** could be done by analogy with the assignment of **6** and other *o*-hydroxyaromatic ketones.[8] Likewise, the assignments of the ^{13}C spectra the naphthalenes **11–15** could be related to the assignment of **9**. The assignment of ^{1}H and ^{13}C spectra of phenanthrenes is usually difficult owing to the nearly identical shifts of H-2, H-3 and H-9 and of C-2, C-3 and C-9 of phenanthrene.[26,27] Based on the coupling patterns, the ^{1}H NMR resonances can be divided into two groups: H-2, H-3, H-6, H-7 in one group and H-1, H-8, H-4, H-5 in the other. The assignment was further supported by HETCOR[28] and COLOC[29] spectra. Cross peaks due to long-range couplings to the OH group permitted unambiguous assignment of C-8a and C-9 in the COLOC spectrum. Substituent effects on chemical shifts derived from **9** and **10** were also used. The position of the second acetyl group of **18** could be assured owing to the chemical shifts and coupling constants of the ^{1}H spectrum. The 6-position is in accord with suggestions by Mosettig and Burger.[30] Finally, a comparison of the ^{13}C chemical shifts of **17** and **18** confirmed the assignments of these two compounds (Table 1).

RESULTS

ΔC(OD)

OD deuterium isotope effects on ^{13}C chemical shifts have been determined for a large array of intramolecularly hydrogen-bonded compounds including naphthalenes.[4,6,8] In Fig. 1, deuterium isotope effects for additional compounds are given to illustrate the effects of steric strain.

The deuterium isotope effects of 2-hydroxy-1-acenaphthone (**9**) are clearly different from those of 1-hydroxy-2-acenaphthone (**8**), the corresponding aldehyde (**7**) and similar compounds.[8] The $^{2}\Delta C(OD)$ value for **9** falls outside the $^{2}\Delta C\text{-}2(OD)$ *vs.* δOH plot (Fig. 2). Other sterically hindered compounds, **2**, **6**, **9**, **11–15**, **17** and **18** show the same feature. This is most evident for the phenanthrene derivatives. Further, the data for the sterically hindered naphthalenes (**9**, **11–15**) are found to fall roughly on one line ($r = 0.94$). The isotope effects at C-1, C-3, C-4, C-7 and C-8 of the sterically hindered naphthalenes (**9**, **11–15**) and the corresponding positions of the phenanthrenes are likewise noteworthy. The negative sign of the isotope effects at the carbonyl carbons is unusual.

$^{n}\Delta C(OD)$ isotope effects on side-chain carbons

The isotope effects observed at the CH_3 carbons of the 1-acetyl groups are numerically larger than those estimated using the plot in Ref. 8. Likewise, the observation of isotope effects at the CH_3 of the propionyl group of **11** and at the CH_2 of the butyryl group of **13** is unusual The effect at 6-CH_3 of **2** is unexpected. No effects are observed at the quaternary carbon of the *tert*-butyl

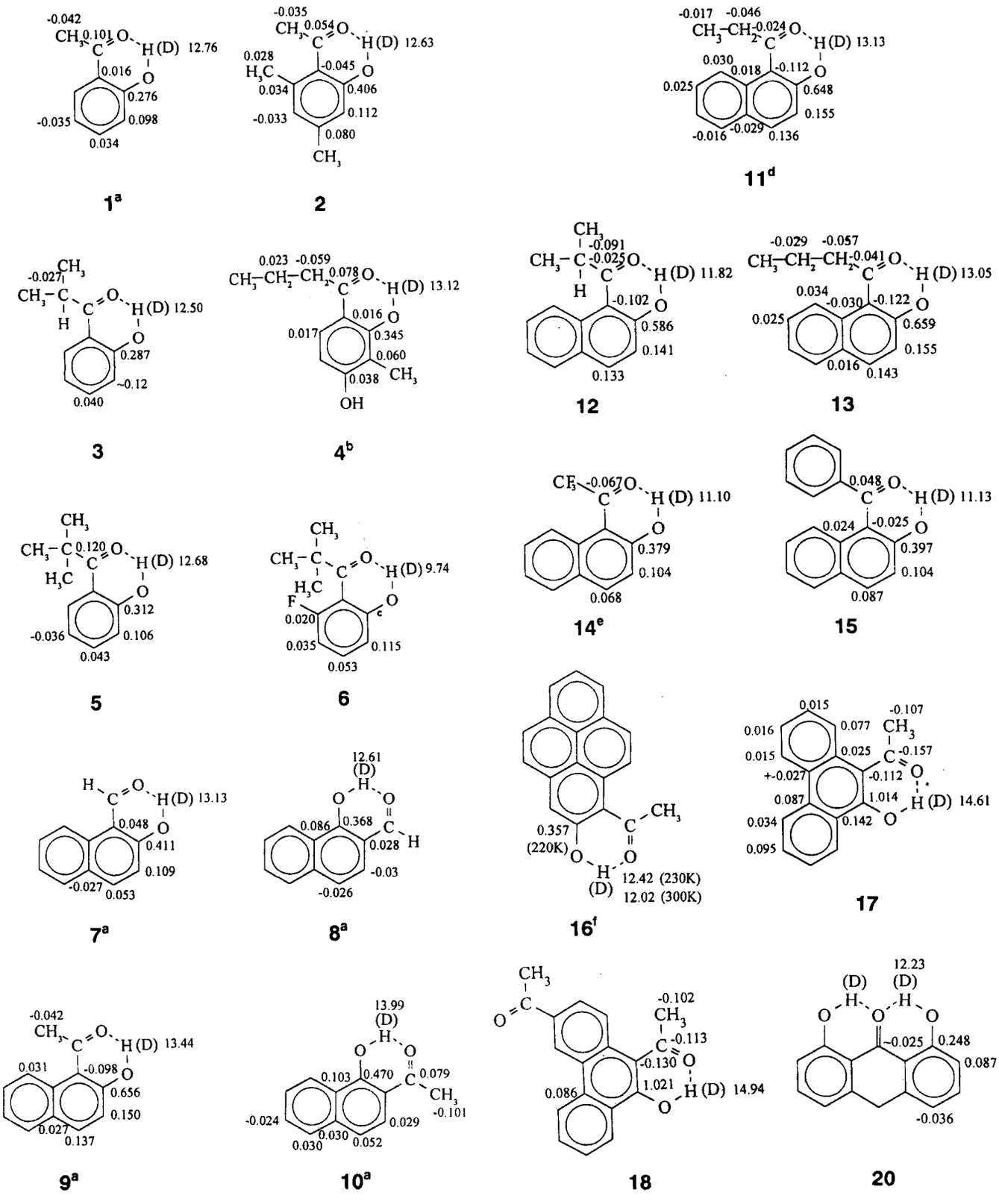


Figure 1. Deuterium isotope effects on ^{13}C chemical shifts, $^{n}\Delta C(OD)$ (in ppm), and ^{1}H chemical shifts (relative to TMS), $\delta(OH)$ (in ppm). (a) Taken from Ref. 8. (b) Two drops of DMSO-d_6 were added. Very similar values were obtained when no DMSO-d_6 was added. (c) Not observed. (d) Measured at 285 K. Values very similar to those obtained at 300 K. (e) Measured at 250 K. (f) Measured at 220 K.

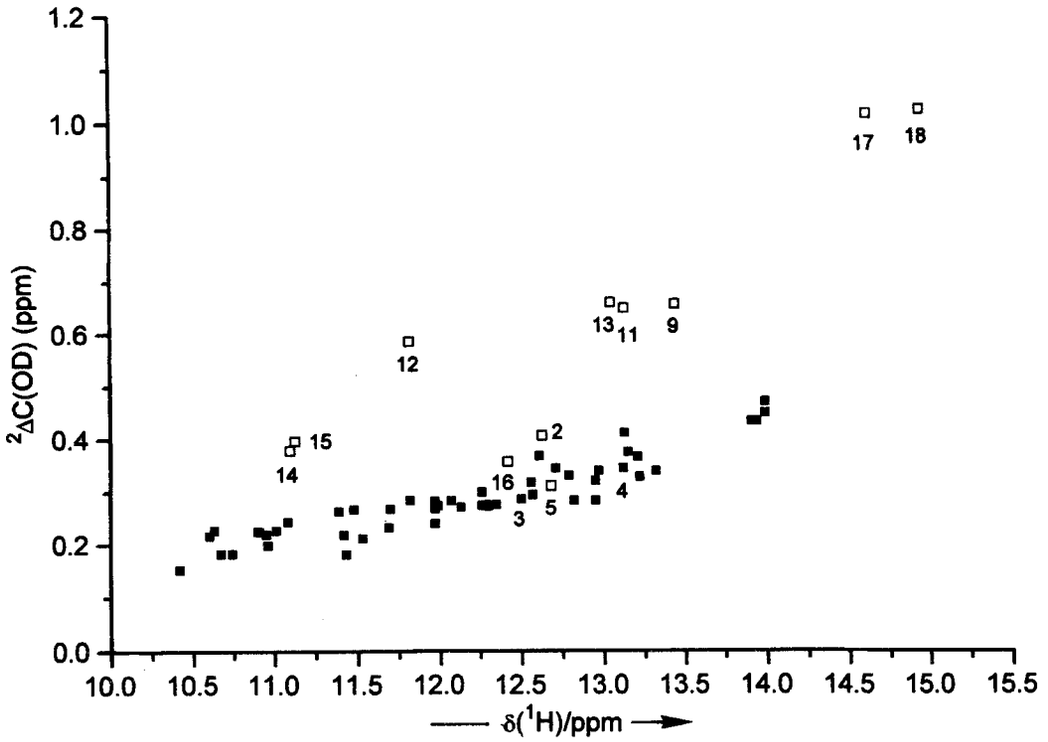


Figure 2. Plot of $^2\Delta C(OD)$ *vs.* $\delta(OH)$ (in ppm) for *o*-hydroxyacyl aromatics. $^2\Delta C(OD)$ values primarily from Ref. 8. Data from this study are marked with numbers. Supposedly sterically hindered compounds are shown as open squares.

group of **5** and **6**. This is in line with findings for enamines,[10] for which it was shown that hyperconjugation played a role for observation of this effect.[12]

Methyl group deuteriation

Prolonged deuteriation at reflux temperature of **9**, **16**, **17** and **18** leads to deuterium incorporation at the methyl group as seen by a diminution of the ^{1}H and ^{13}C methyl resonances and observation of an isotope effect shifted triplet or multiplet in the ^{13}C spectrum depending on the degree of deuterium incorporation. $^1\Delta C(D)$ is large, *ca.* 0.25 ppm, whereas the two-bond isotope effect at the carbonyl carbon is small and only observable at high degrees of deuteriation. In addition to small two-bond isotope effects at the methyl proton resonances, prominent negative isotope effects are observed at the OH resonances (Fig. 3). The effects per deuterium are not additive (−0.0113, −0.0108 and −0.0104 ppm, the largest value being obtained for monodeuteriation). The magnitude of monodeuteriation is slightly larger for **16** (−0.0146 ppm, 230 K) than for **17**, but similar for **9** (−0.0110 ppm), **17** and **18**. No isotope effects on OH chemical shifts were observed for compounds such as 5-fluoro-2-hydroxyacetophenone or 6-methoxy-2-hydroxyacetophenone.[8]

Carbon–fluorine and proton–fluorine coupling constants

These couplings in **6**, **14** and **19** show some interesting features (Fig. 4). Through-space couplings are observed between the fluorine and the hydrogen and the carbon of the CH_3 group of **6**. The corresponding couplings are much smaller in **19**. For **6** $J(CH_3, F)$ increases slightly,

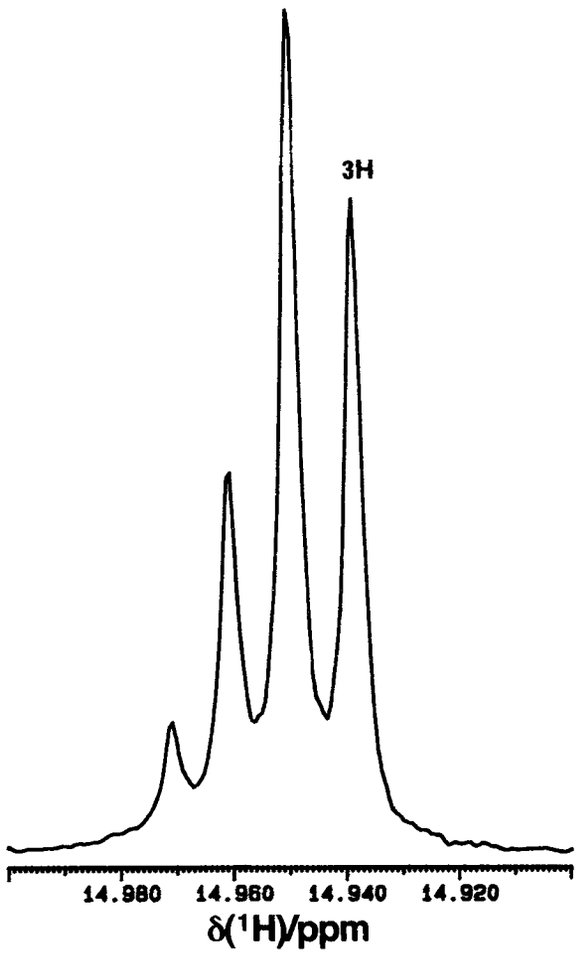


Figure 3. ^{1}H NMR spectrum of the *OH* resonance of **18** deuteriated at the CH_3 group. The resonance belonging to the non-deuteriated species is marked as 3H.

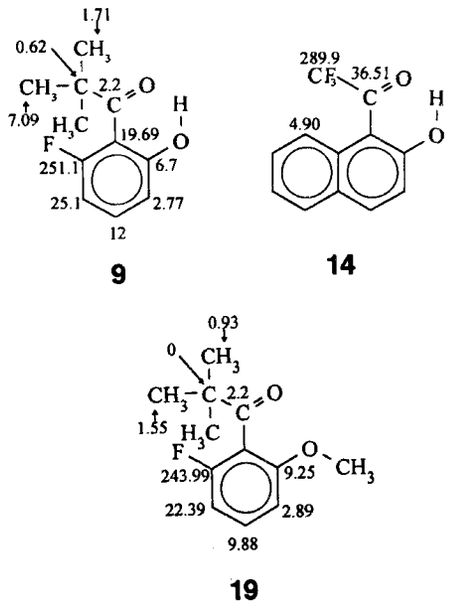


Figure 4. Carbon–fluorine and proton–fluorine coupling constants (in Hz) of model systems.

from 7.09 to 7.57 Hz, on lowering the temperature from 300 to 215 K. This coupling decreases marginally to 6.92 Hz on deuteriation of the OH proton. This value is an upper limit as only 30% deuteriation was achieved and separate resonances from the H and D species could not be obtained.

Temperature effects

The ^{13}C chemical shifts of **2**, **11** and **17** were measured as a function of temperature. Only very moderate changes were observed. For **17** the C-10 carbon chemical shift was found to change by 0.0029 ppm K^{-1} ($r = 0.999$) and C-15 by 0.0037 ppm K^{-1} ($r = 0.997$). Likewise, the isotope effects of **17** did not change much with temperature; $^2\Delta$C-10(OD) changed by 2.66×10^{-4} ppm K^{-1} ($r = 0.994$). This is in accord with observations made for **1**.[7]

OH chemical shifts

Slow exchange on the NMR time-scale is essential for the correct measurement of isotope effects. Intermolecular exchange is a possible source of error, especially in the strongly sterically hindered compounds. Thorough purification is very important for minimizing intermolecular exchange. For **14** a sharp OH resonance could only be obtained at 250 K.

Temperature coefficients for the OH chemical shifts of **2**, **6**, **11**, **14** and **17** were obtained by plotting chemical shifts *vs.* temperature in the range 240–300 K. Measurements were performed at lower temperatures, but the curves showed a tendency to level off at the low temperatures. In the following a comparison of δ(OH) and changes in ppm K^{-1} is given: **6**, 9.74, 0.0099; **14**, 11.10, 0.0088(5); **2**, 12.63, 0.0084; **11**, 13.13, 0.0075; **27**, 13.21, 0.0047; **1**, 12.76, 0.0025; **17**, 14.61, 0.0022. These changes per degree may be compared with the value for the hydrogen-bonded OH group of 2,6-dihydroxyacetophenone at low temperature and measured in CD_2Cl_2, 0.0146 ppm K^{-1}. The general trend is that the largest temperature coefficients are obtained for compounds with weak hydrogen bonds, as evidenced from low OH chemical shifts.

$^1\Delta^{13}C(^{18}O)$

The one-bond isotope effects for hydrogen-bonded ketones are in the range 42–32 ppb (Table 2). This range

Table 2. One- and two-bond ^{18}O isotope effects on ^{13}C chemical shifts (in ppb) of carbonyl carbons

Compound	$^1\Delta^{13}C(^{18}O)$	$^2\Delta^{13}C(^{18}O)$
Acetophenone (**21**)[a]	47.1	0
2-Hydroxyacetophenone (**1**)	41.6 ± 0.9	7.0 ± 0.2
4-Hydroxyacetophenone (**22**)[a]	44.0	0
4-Methoxyacetophenone (**23**)[a]	45.8	0
2,4-Dihydroxyacetophenone (**24**)	38.6 ● 0.1	8.3 ± 0.6
2-Hydroxy-4-methoxyacetophenone (**25**)	40.3 ± 0.9	7.6 (5) ± 0.5 (5)
2,6-Dihydroxyacetophenone (**26**)	41.5 (5) ● 0.2 (5)	8.2 (5) ± 0.1 (5)
2-Hydroxy-6-methoxyacetophenone (**27**)	40.4 ± 0.2	8.2 ± 0.8
2,4-Dihydroxy-3-methylbutyrophenone (**4**)	39.9 ± 0.4	7.5 ± 0.2
Benzophenone (**28**)[b]	46	0
2-Hydroxybenzophenone (**29**)	40.6 (5) ± 0.35	7.1 ± 0 (C-1) 2.8[c] (C-1′)
2,2′-Dihydroxybenzophenone (**30**)	38.7 ± 0.2	n.o.[d]
2,2′-Dihydroxybenzophenone (**30**)[e]	41.4[f]	n.o.[d]
2,2′-Dihydroxy-4,4′dimethoxybenzophenone (**31**)	32.7 ± 0.4	3.5[c]
1-Hydroxy-2-acenaphthone (**10**)	38.7 ± 0	7.9 ± 0.3
2-Hydroxy-1-acenaphthone (**9**)	40.0 (5) ± 0.2 (5)	9.1 (5) ± 0.0 (5)

[a] Values taken from Ref. 17.
[b] Value taken from Ref. 36.
[c] Seen as a shoulder.
[d] Not observed.
[e] DMSO added (see text).
[f] Only one measurement.

can be compared with the value for acetophenone (**21**) of 47.0 ppb[31] and acetophenones in general.[16,17,31] The introduction of an *o*-hydroxy group leads to a decrease in the magnitude, as seen from the following pairwise comparisons: acetophenone (**21**), 47.0 ppb,[31] and *o*-hydroxyacetophenone (**1**), 41.8 ppb (difference, 5.2 ppb); 2,4-dihydroxy- (**24**), 38.6 ppb, and 4-hydroxy- (**22**),[31] 44.0 ppb (difference, 5.4 ppb); and 2-hydroxy-4-methoxy- (**25**), *ca.* 40 ppb and 4-methoxy- (**23**),[31] 45.8 ppb (difference, *ca.* 5.8 ppb). A methoxy or a hydroxy group in the *para* position has a smaller effect than in the *ortho* position. The effect of a 4-methoxy group is 1.3 ppb and that of a 4-hydroxy group is 2.7 ppb. The larger decrease caused by an *o*-hydroxy group, which forms an intramolecular hydrogen bond, shows that hydrogen bonding leads to an extra decrease in the one-bond isotope effect, $^1\Delta^{13}C(^{18}O)$. Introduction of a hydroxy group in the 6-position has hardly any effect at all [the difference between 2,6-dihydroxy- (**26**) and 2-hydroxyacetophenone (**1**) is 0.1 ppb], whereas a methoxy group in this position leads to a decrease of 2.6 ppb.

C=O chemical shifts and $^1\Delta^{13}C(^{18}O)$ isotope effects are correlated. A literature study[13] indicated that intramolecular hydrogen-bonded compounds would fall outside this correlation. This has been tested further in this study. *C*=O chemical shifts and one-bond $^1\Delta^{13}C(^{18}O)$ isotope effects for intramolecularly hydrogen-bonded compounds without severe steric strain are included in Fig. 5. It is seen that the data points fall below the line. It is also seen from Fig. 5 that the formation of a second hydrogen bond has a much smaller effect than the formation of the first hydrogen bond.

$^2\Delta^{13}C(^{18}O)$

Isotope effects over two bonds have been reported only in very few cases and not for acetophenones.[16,31] In the present compounds, two-bond isotope effects are observed at C-1 or at C-1′. For those detected, the magnitudes fall in the range 2.8–9.3 ppb.

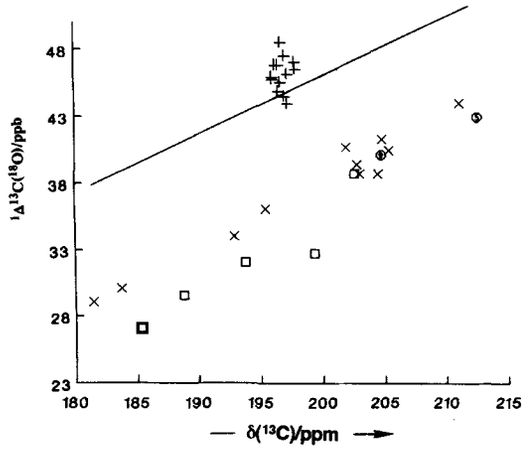


Figure 5. Plot of $^1\Delta^{13}C(^{18}O)$ (in ppb) *vs.* the ^{13}C chemical shift of carbonyl carbons, $\delta(C{=}O)$ (in ppm). The straight line is based on values from Ref. 13. +, Ketones without hydrogen bonds; X ketones with one hydrogen-bond; ○, sterically hindered ketones with one hydrogen bond; □, ketones with two hydrogen bonds.

DISCUSSION

The unusually large two-bond isotope effects, $^2\Delta C(OD)$, observed in the sterically hindered compounds (**2**, **6**, **9**, **11–18**) combined with the unusual isotope effects observed at the positions shown in Fig. 6 can be explained as a function of steric strain and intramolecular hydrogen bonding. The carbonyl group points towards the OH group, thereby leaving the CH_3 (or alkyl) group to point towards the *peri*-proton (H-8 for naphthalenes and H-10 for phenanthrenes). A fine balance exists between a planar structure to optimize the strength of the hydrogen bond and the tendency to twist the carbonyl group to minimize steric strain. By deuteriation the hydrogen bond is weakened[32] and this allows the carbonyl group to twist further, causing a change in the chemical shifts. The changes in the chemical shifts are in agreement with an increase in the twist angle. C-2 and C-4 are in conjugation with the carbonyl group. The carbonyl group is clearly twisted out of the plane (Fig. 7). Such a twist causes a decrease in conjugation and a high-field shift at positions C-2 and C-4.[33] Further, a low-field shift of the carbonyl carbon is expected.[34] The unusual isotope effects are seen at those carbons and in the correct direction. Such a steric relaxation model is also supported by the change in the $J(CH_3,F)$ coupling of **6**. By deuteriation of the OH group, the through-space carbon–fluorine coupling is diminished, supporting a sligthly larger twist angle. The opposite result is obtained by cooling (as the twist angle in that case is reduced leading to a larger through space coupling).

Such a model can also explain the isotope effect at the methyl group in the 6-position of **2**. This methyl group is close to the $CH_3C{=}O$ group and therefore sensitive to changes in the twist angle. Further, the twist of the carbonyl group resulted in a high-field position of the 6-CH_3 methyl group (Table 1). Further twist due to deuteriation will therefore lead to a further high-field shift and a positive isotope effect.

Deuteriation of the CH_3 group of **9**, **16**, **17** and **18** leads to a low-field shift of the OH resonance. This can also be seen as a steric effect. The CD_3 group is, on

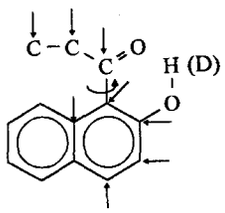


Figure 6. Positions showing large steric isotope effects.

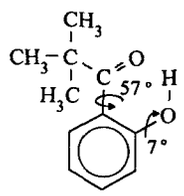


Figure 7. Twist angles for **3**. Corresponding carbonyl twist angles are as follows: for **1**, 24.7°; for **2**, 51.4°; and for **6**, 60.7° (calculated using the MM2 program[43,44]).

average, slightly smaller than the CH_3 group. This lowers the strain and hence decreases the twist angle. A smaller twist angle leads to a stronger hydrogen bond. This leads to a low-field shift and therefore to a negative isotope effect at the OH proton.

The two-bond isotope effects, $^2\Delta C(OD)$, are very large in **17** and **18**. The magnitudes suggest that a tautomeric equilibrium may occur. Temperature studies of isotope effects of **17** showed only small changes in the isotope effects (see Results). The effect of 2.66×10^{-4} ppm K^{-1} can be compared with 1.2×10^{-4} ppm K^{-1} for **1**[7] (non-tautomeric) and 3.8×10^{-3} ppm K^{-1} for the β-diketone 2-acetylcyclohexan-1-one (tautomeric),[6] thus ruling out tautomerism.

$^1\Delta^{13}C(^{18}O)$

The suggestion that hydrogen bonding influences $^1\Delta^{13}C(^{18}O)$ is further supported by the qualitative trends between $^1\Delta^{13}C(^{18}O)$ and $^2\Delta C(OD)$ and between $^1\Delta^{13}C(^{18}O)$ and $\delta(OH)$ (no straightforward correlations are obtained). Both $\delta(OH)$ and $^2\Delta C(OD)$ are measures of hydrogen bond strength and as they become larger, $^1\Delta^{13}C(^{18}O)$ simultaneously decreases. This is also seen for the corresponding *o*-hydroxysalicylaldehydes and -salicylic esters (Fig. 6 in Ref. 14), as hydrogen bonding generally is weaker in these compounds compared with the hydrogen-bonded ketones. The decrease in $^1\Delta^{13}C(^{18}O)$ can be understood as resonance assistance,[35] leading to a decrease of the double bond order of the C-1—C=O bond.

The change from intramolecular to intermolecular hydrogen bonding can be seen for 2,2′-dihydroxybenzophenone (**30**). In $CDCl_3$ and CD_2Cl_2 the intramolecular hydrogen bond is intact, whereas if DMSO-d_6 is added, the hydrogen bonding type changes to intermolecular hydrogen bonding. This is seen from δ(OH), which changes from 10.66 to 10.87 ppm on addition of DMSO-d_6. $^1\Delta^{13}C(^{18}O)$ changes likewise from 38.7 ppb in CD_2Cl_2 to 41.4 ppb (Table 2). This increase is due to breaking of the intramolecular hydrogen bond and thus supports the finding that intramolecular hydrogen bonding of the RAHB (resonance-assisted hydrogen bonding)[35] type leads to a decrease in the one-bond isotope effect.

$^2\Delta^{13}C(^{18}O)$

The acetophenones, C-1 of 2-hydroxybenzophenone (**29**) and the hydroxyacenaphthones show values of 6.9–9.3 ppb (Table 2). The large value to C-1 and not to C-1′ of **29** shows clearly that the large values are related to hydrogen bond formation. Hydrogen bonding, as seen for $^n\Delta C(OD)$ isotope effects, leads to an increase in isotope effects for carbons on the pathway involved in hydrogen bonding. This is a consequence of RAHB. The latter will increase the double bond order of the C-1—C=O bond and hence lead to an increase in the two-bond ^{18}O isotope effect to C-1, which is part of the RAHB system,[35] but not to C-1′. The finding that no values are reported for acetophenones in general supports this conclusion.

Structural studies

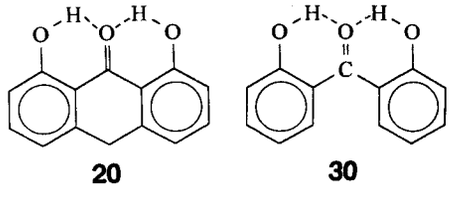
1,8-Dihydroxyanthraquinone and the related compound averufin are planar molecules with two hydroxy groups forming hydrogen bonds to one acceptor (Fig. 8). Compound **30**, 2,2′,4,4′-tetrahydroxybenzophenone and **31** also have this feature. In addition, they are non-planar. This twist of the benzene rings may influence the hydrogen bond pattern. The x-ray structure of **29**[23] shows the interesting feature that one C=O···H—O bond is relatively short, whereas the other is long. It has also been claimed that both OH bonds are not formed simultaneously.

The structure of the hydroxybenzophenones can be described by the parameters $\delta(OH)$, $^n\Delta C(OD)$ and $^n\Delta^{13}C(^{18}O)$. The OH resonances and the C-1, C-1′ carbon resonances are single resonances for both the hydroxyanthraquinones and -benzophenones mentioned above. This indicates that averaging takes place on the NMR time-scale.

For **29**, the magnitude of $^2\Delta$C-2(OD) shows that the hydrogen bond strength is normal, whereas for **30** the hydrogen bond is weak, as judged both from $\delta(OH)$, $^2\Delta$C-2(OD) and from the OH proton, which shows a tendency for intermolecular OH exchange in chloroform. For **31**, the hydrogen bond is stronger owing to the 4-methoxy group. A similar increase is also found for the acetophenones.

1,8-Dihydroxyanthraquinone and **20** show small $^2\Delta C(OD)$ values. The general picture is that the formation of two hydrogen bonds to the same acceptor leads to relatively weak hydrogen bonds.

Deuteriation of the OH group leads for both 1,8-dihydroxyanthraquinone and **31** to a relay isotope effect at the other OH hydrogen. No such effect is observed in **30**, probably owing to the weak hydrogen bond. Similar isotope effects are also observed in 2-hydroxybenzoylbenzoylmethane and in tetracycline.[12] The C-1′ carbon of **31** also shows a long-range isotope effect, but **20** and 1,8-dihydroxyanthraquinone do not.[6] The observation of an isotope effect on the OH resonance can be explained in a way similar to the strain isotope effect discussed for **2**, **5**, **6**, **9** and **10**–**17**. Deuteriation of one OH group and the connected weakening of the hydrogen bond in which deuterium takes part lead to a strengthening of the non-deuteriated C—OH(1′)···O=C hydrogen bond. This leads to a low-field shift of the 1′-OH proton and hence to a negative isotope effect. This strengthening can also lead to a decrease of the twist angle and therefore to a low-field shift of the C-1′ resonance. This explanation is supported by the fact that the planar and rigid 1,8-dihydroxyanthraquinone shows no isotope effect at C-8, but the non-planar tetracycline shows remote isotope effects.[12]



20 **30**

Figure 8. Model compounds with two hydrogen bonds to the same acceptor.

The isotope effects on OH chemical shifts show unambiguously that both OH groups form simultaneous hydrogen bonds. This is also confirmed by the magnitude of $^1\Delta^{13}C(^{18}O)$ (see above).

The twist angle is clearly different for different compounds. The $^1\Delta^{13}C(^{18}O)$ value for **28** (46 ppb)[36] can be compared with that of C-10 of averufin (planar) (41.7 ppb),[31] whereas the value for **31** can be compared with C-9 of averufin (29.5 ppb).[31] In both cases, the benzophenone values are higher owing to twist.

The combination of ^1H and ^{13}C chemical shifts and deuterium and ^{18}O isotope effects on these provides a qualitative picture of the structure of *o*-dihydroxybenzophenones as follows: both OH groups form hydrogen bonds simultaneously, both hydrogen bonds are weaker than in similar compounds with only a single hydrogen bond to the acceptor and both phenyl groups are twisted.

Recently, Al-Rashid and El-Bermani[37] claimed, based on infrared studies, that **1** exists as a mixture of a *cis* and a *trans* form with the latter dominating. For *o*-hydroxypropiophenone, *o*-hydroxybutyrophenone and **3** both the *cis* and *trans* forms were observed together with other forms. These results disagree with the present findings. For **1**, *o*-hydroxypropiophenone,[8] **3** and **4** (similar to *o*-hydroxybutyrophenone), the intramolecularly hydrogen-bonded form (called *cis* above) is clearly dominant.

$^1\Delta^{13}C(^{18}O)$ *vs.* $\delta(^{17}O)$

Hydrogen bonding has a dramatic effect on ^{17}O chemical shifts as shown by St Amour *et al.*[38] Hydrogen bonding and twist counteract each other for ^{17}O chemical shifts in *o*-hydroxybenzamides.[39] As a similar behaviour is observed for $^1\Delta^{13}C(^{18}O)$, a comparison of these two parameters seems of interest. A very useful equation correlating $^1\Delta^{13}C(^{18}O)$ and ^{17}O chemical shifts have been derived by Risley.[18] The equation is based on a variety of compounds including acetophenones. Unfortunately, very few data for compounds with steric strain or intramolecular hydrogen bonds are included in the correlation. The present data enable this equation to be tested for such compounds.

In Fig. 9, only aromatic ketones are included. The correlation is good for most compounds. However, two compounds, **9** and **30**, fall outside the correlation. For **30**, the value with DMSO added is clearly far off, as the corresponding ^{17}O chemical shift is measured in a non-polar solvent. The correlation coefficient without the latter datapoint is 0.95, slope 0.078 and intercept at *y*-axis 3.2 compared to the correlation found by Risley for a wider range of compounds[18] (0.82, 0.51 and 18.2). The sterically hindered **9** falls below the line. Steric hindrance does not perturb $\delta(^{17}O)$ and $^1\Delta^{13}C(^{18}O)$ in the same manner. Despite the small variation in $^1\Delta^{13}C(^{18}O)$ isotope effects, this remains a very useful parameter, which cannot automatically be replaced by measurement of ^{17}O chemical shifts.

EXPERIMENTAL

NMR experiments

The ^{13}C NMR spectra of deuteriated species were recorded in $CDCl_3$ on a Bruker AC 250 NMR spectrometer at 725.79 MHz with a digital resolution of 0.55 Hz per point. Chemical shifts were measured relative to internal TMS. Spectra were recorded at 300 K and in $CDCl_3$ unless stated otherwise. Spectra of both deuteriated and non-deuteriated species and of mixtures of the two species were recorded for all compounds.

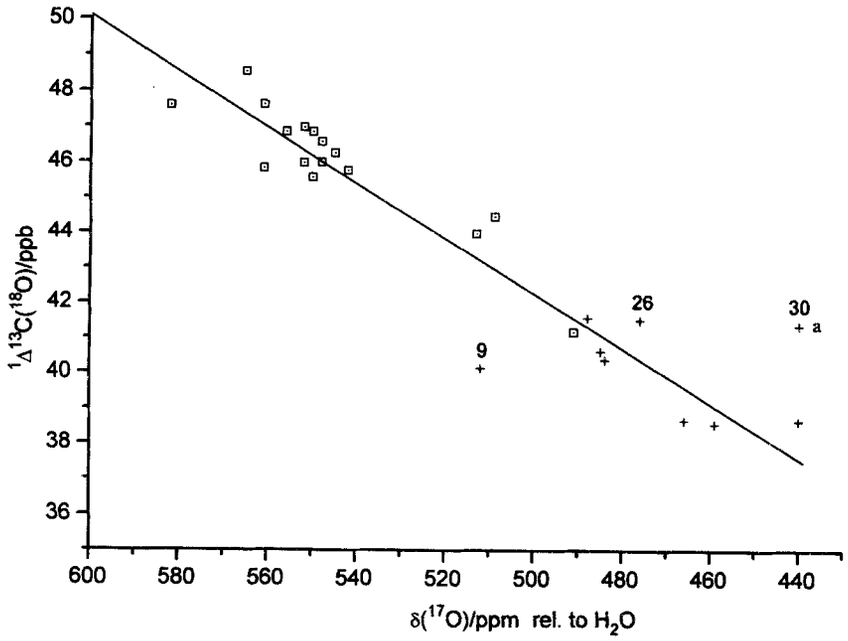


Figure 9. Plot of $^1\Delta^{13}C(^{18}O)$ (in ppb) *vs.* the ^{17}O chemical shift, $\delta(^{17}O)$ (in ppm). Isotope effects $^1\Delta^{13}C(^{18}O)$ from Ref. 16, if not from this study. ^{17}O chemical shifts taken from Ref. 39.[a] With DMSO added. +, hydrogen-bonded carbonyl compounds (**1**, **9**, **10**, **21–24**, **26**, **27**, **29** and **30**). □, carbonyl compounds without hydrogen bond mainly *o*-hydroxyacetophenones plus benzophenone and anthrone.

HETCOR[28] and COLOC[29] spectra were recorded as described in Ref. 7.

The ^{13}C NMR spectra of ^{18}O-enriched compounds were recorded at 93 MHz on a Bruker AM500 instrument at a digital resolution of 0.23 Hz per point. The results are normally the averages of three measurements.

Compounds

2-Hydroxyisobutyrophenone (**3**) was synthesized according to Briggs *et al.*[40]

Synthesis of 2-hydroxypivalophenone (**5**) was attempted in the same manner, but resulted in a very low yield. A better approach is to treat 2-methoxybenzoic acid with a threefold excess of *tert*-butyllithium in pentane as described in Ref. 41. This leads to a mixture of **5** and 2-methoxypivalophenone. The former can be isolated by extraction with 1 M sodium hydroxide solution and the latter can be transformed into the former by treatment with an equimolar amount of dry aluminium chloride in CS_2 overnight. The yield was 60%.

6-Fluoro-2-hydroxypivalophenone (**6**) was prepared by treatment of 6-fluoro-2-methoxybenzonitrile with a threefold excess of *tert*-butyllithium in pentane for 1 h.[41] After hydrolysis in 10% HCl, 6-fluoro-2-methoxypivalophenone was obtained. Treatment with a large excess of dry aluminium chloride in CS_2 overnight transformed it into a mixture of **6**, **5** and **19** in the ratio 1 : 1 : 4' The phenols, **5** and **6**, were extracted with 1 M sodium hydroxide solution and separated on a pressure column (1.5–2 atm) of silica gel (15 μm) with a mobile phase of hexane–chloroform–methanol (4 : 1 : 0.5). Compound **6** was sublimed on to a cold-finger at 50 °C and 0.1 mbar. The yield was *ca.* 1%.

4,6-Dimethyl-2-hydroxyacetophenone was prepared according to Clark and Miller.[24]

2-Hydroxy-1-propionylnaphthalene (**11**) was prepared by treatment of 2-methoxynaphthalene with propionyl chloride and $AlCl_3$ in CS_2 according to Fuson and Chadwick,[42] except that the reaction mixture was refluxed for 2 h. Propionic acid was removed by extraction with saturated K_2CO_3 solution. The produce contained four major species, as seen from GC–MS, all having one propionyl group. Only **11**, being a naphthol, was extracted into 1 M sodium hydroxide solution. The product was recrystallized from cyclohexane; m.p. 78.8–79.8 °C. The yield was 30%.

2-Hydroxy-1-benzoylnaphthalene (**15**) was synthesized in analogy to **11** using benzoyl chloride. The product was purified by precipitation from an acetone solution by addition of water; m.p. 136.7–137.1 °C. The yield was 50%.

2-Hydroxy-1-isobutyrylnaphthalene (**12**) was prepared in the same manner using isobutyryl chloride. The raw product contained four major species, 2-methoxynaphthalene and three species with one isobutyryl group. Compound **12** was only a minor fraction. The raw product was refluxed with 3 equimolar amounts of dry aluminium chloride in CS_2 overnight. Half of the 2-methoxy-1-butyrylnaphthalene was transformed into **12**. The naphthols were extracted and separated as described for **11**. Compound **12** was further purified by base extraction/acid precipitation. A pure oil was obtained in 2% yield.

2-Hydroxy-1-butyrylnaphthalene (**13**) was made analogously using butyric anhydride. The oil was distilled under reduced pressure (0.1 mbar). The yield was 20%.

2-Hydroxy-1-trifluoroacetylnaphthalene (**14**) was synthesized similarly using trifluoroacetic anhydride. The product was sublimed on to a cold-finger at 50 °C and 0.1 mbar; m.p. 62.5–63.1 °C. The yield was 5%.

9-Acetyl-10-hydroxyphenanthrene (**17**) and 6,9-diacetyl-10-hydroxyphenanthrene (**18**) were prepared by a Friedel–Crafts reaction according to Mosettig and Burger.[30] The reactions mixture was degassed with nitrogen to avoid oxidation before addition of the acetyl chloride over a period of 20 min. The product was a mixture of four major compounds, the 9,10-quinone, 9-hydroxyphenanthrene, **17** and **18**. The amount of quinone could be minimized by prolonged degassing, but no avoided. The ratio of the three other compounds varied according to the amount of acetyl chloride added, and the 9-hydroxyphenanthrene could be eliminated by addition of three equimolar amounts of acetyl chloride. The compounds were separated on a pressure column (1.5–2 atm) of silica gel (15 μm) using a mobile phase of hexane–chloroform–methanol (4 : 1 : 0.5). Compound **18** was eluted first. The pure fractions were recrystallized from cyclohexane; m.p. of **18**, 179.1–179.6 °C.

Reagents were purchased from Aldrich (Weinheim, Germany) and used without further purification.

^{18}O incorporation

^{18}O incorporation was achieved in dioxane by addition of ^{18}O-enriched water (90%) together with traces of concentrated HCl as catalyst. A 40 mg amount of compound is usually dissolved in 1 ml of dioxane and 100 μl of $H_2{}^{18}O$ (90%) and 10 μl of concentrated HCl are added. The sample is stirred for 3 days and the dioxane and water are evaporated by heating in a stream of nitrogen. Typical levels of incorporation are 35–60%.

Acknowledgements

The authors thank Morten Langgård and Birgit Andresen for performing the MM2 calculations. They also thank the Danish Natural Science Research Council for the use of the Bruker AM 500 NMR spectrometer at the Technical University of Copenhagen.

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