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Tautomerism of Enolic Triacetylmethane, 2-Acyl-1,3-cycloalkanediones, 5-Acyl Meldrum's Acids and 5-Acyl-1,3-dimethylbarbituric Acids studied by means of Deuterium Isotope Effects on ^{13}C Chemical Shifts

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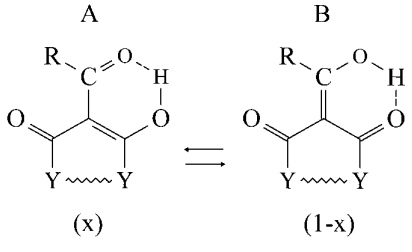
ABSTRACT: Deuterium isotope effects on ^{13}C nuclear shielding, $^{n}\Delta C(OD)$, were investigated for a series of enolic triacetylmethane, 2-acyl-1,3-cycloalkanediones, 5-acyl Meldrum's acids and 5-acyl-1,3-dimethylbarbituric acids at different temperatures. The enolic 2-acyl-1,3-cycloalkanediones, 5-acyl Meldrum's acids and 5-acyl-1,3-dimethylbarbituric acids all exhibit intramolecular enol–enol tautomerism. For the first two the equilibrium constants were estimated from the deuterium isotope effects on the enolic and carbonylic carbons. The equilibrium constants were estimated to be 1.5 for the enolic 2-acyl-1,3-cyclohexanediones and 2-acetyl-1,3-cyclopentanedione, favouring the form having an endocyclic enolic double bond, and 0.8 for 5-acyl-1,3-dimethylbarbituric acids, favouring the form having an exocyclic enolic double bond. Apparently, the equilibrium position is unaffected by increasing the size of the acyl group, and therefore no distinct effects caused by steric hindrance were observed. The non-hydrogen-bonded α-carbonyl group of enolic triacetylmethane, the 2-acyl-1,3-cycloalkanediones, 5-acyl Meldrum's acids and 5-acyl-1,3-dimethylbarbituric acids cause a high frequency shift of the OH ^{1}H chemical shifts. A plot of the latter against the sum of $^{2}\Delta C(OD) + {}^{4}\Delta C(OD)$ shows a larger sum for the compounds apparently exhibiting intramolecular enol–enol tautomerism than for compounds apparently not exhibiting such tautomerism. © 1998 John Wiley & Sons, Ltd.

KEYWORDS: deuterium isotope effects; chemical shifts; equilibrium isotope effects; variable-temperature NMR; tautomerism; triacetylmethane; 2-acyl-1,3-cycloalkanediones; 5-acyl Meldrum's acids; 5-acyl-1,3-dimethylbarbituric acids

INTRODUCTION

2-Acyl-1,3-cycloalkanediones,[1,2] 5-acyl Meldrum's acids,[3,4] 5-acyl-1,3-dimethylbarbituric acids[5] and 4-propionylisochroman-1,3-diones[6] are only observed in the enolic form, whereas triacetylmethane, **7** (see Scheme 1), is reported to exist in both the enolic and keto forms.[7,8]

The aim of this investigation was to determine whether enolic 2-acyl-1,3-cycloalkanediones, (**1–6**, **8**), triacetylmethane (**7**), 5-acyl Meldrum's acids (**9–13**), 5-acyl-1,3-dimethylbarbituric acids (**14–16**) and 4-propionylisochroman-1,3-diones (**17**) display intramolecular enol–enol tautomerism. Compounds **1–8** have earlier been found to be tautomeric[2] (Fig. 1). Compound **17** is reported to be in the exocyclic enolic form [Fig. 1(B)] in solution and in the endocyclic enolic form [Fig. 1(A)] in the solid state.[9] This has been interpreted as if **17** displays enol–enol tautomerism.[6] Tautomerism is not immediately apparent in the NMR spectrum, since a weighted average spectrum of two potentially interchanging forms is expected to be observed. Deuterium isotope effects have been suggested for monitoring the existence of fast equilibria in carbocationic[10] and tautomeric systems.[11] Exchange of a hydrogen with deuterium perturbs the equilibrium, leading to equilibrium isotope effects which are often large compared with the intrinsic isotope effects. The magnitude of the equilibrium isotope effect depends on two factors: (i) the difference in the nuclear shielding of the two equilibrating nuclei in question[10,11] and (ii) the change in the equilibrium constant, K_{eq}, upon deuteration.[10,11] The change in equilibrium constant upon deuteration evidently depends on the position of the equilibrium.[12,13]



Y = C, O or N
R = H, Me, Et, iPr, t-Bu, Ph-CH_2- or 4-NO_2-C_6H_4

Figure 1. Tautomerism of enolic 2-acyl-1,3-cycloalkanediones (Y = C), 5-acyl-barbituric acids (Y = N) and 5-acyl Meldrum's acids (Y = O).

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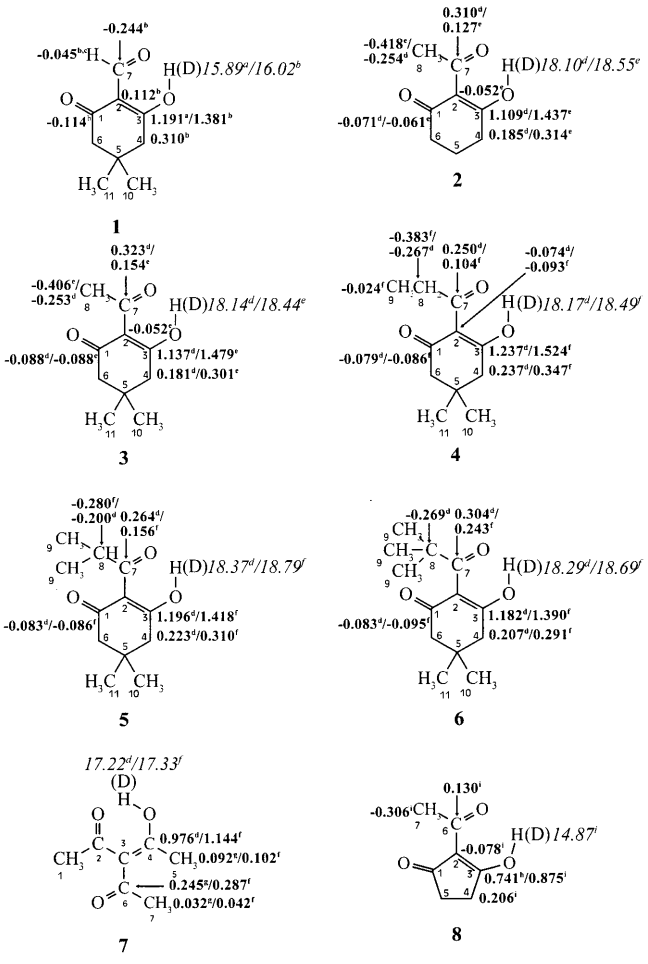


Scheme 1. Deuterium isotope effects on ^{13}C chemical shifts in ppm. The dominant tautomer in $CDCl_3$ or CD_2Cl_2 at 300 K is shown, if nothing else is stated. ^1H OH chemical shifts are given in italics. Data for **18** were taken from Ref. 17. Note that the arrows are incorrect in Ref. 17. Hydrogen bonds (see Fig. 1) are not included for reasons of clarity. Superscript letters: [a] 250 K; [b] 200 K; [c] isotope effect on ^1H; [d] 300 K; [e] 220 K; [f] 230 K; [g] 260 K; [h] 190 K; [i] 170 K; [j] 215 K; [k] 270 K.

The isotope effects are defined as $^n\Delta C(D) = \delta C(H) - \delta C(D)$, where n is the number of bonds between the carbon in question and the deuterium. Large isotope effects on ^{13}C chemical shifts, $^n\Delta C(OD)$, with both positive and negative signs, have been reported for compounds displaying enol–enol tautomerism.[1,11,14–21] The sum of the isotope effect on the enolic and carbonylic carbons, $\Delta_{sum} = {}^2\Delta C(OD) + {}^4\Delta C(OD)$, is independent of the equilibrium contribution and increases with increasing ^1H OH chemical shifts;[13,22] this sum is a possible indicator of intramolecular enol–enol tautomerism.

An interesting feature of the acyl Meldrum's acids and the acyl-1,3-dimethylbarbituric acids is the possibility that the ester and amide carbonyl groups occur enolized. A comparable case is 3,5-diacetyltetrahydropyran-2,4,6-trione[17,23] (**18**), in which the carboxylic carbon involved in the tautomerism is part of an anhydride moiety.

Another important factor also related to tautomerism is the strength of the hydrogen bond, which can be determined either from the ^1H OH chemical shifts[24] or from the two bond deuterium isotope effects on ^{13}C chemical shifts.[25,26]

RESULTS

Chemical shifts

^1H OH chemical shifts. The ^1H OH chemical shifts are presented in Scheme 1. The ^1H OH chemical shifts are shifted to higher frequency upon cooling (as can be seen from Scheme 1) and with negative temperature coefficients (Table 1).

Only enolic forms of **1–6** and **8–16** are observed, in agreement with earlier reports.[1–5] For **7** both an enolic and a triketonic form were present at ambient temperature in $CDCl_3$. However, the enolic form became more abundant upon cooling or on dissolving in and evaporation of methanol.

For enolic 2-acyl-1,3-cyclohexanediones **2–6**, the ^1H OH chemical shifts are between $\delta = 18.10$ and 18.37, $\delta = 16.02$ being found for **1**, 17.22 for **7** and 14.87 for **8**, in accord with earlier findings.[1,2,7,27] The ^1H OH resonances for **1** and **8** are exchange-broadened at 300 K, but become sharp at 250 and 200 K, respectively. Earlier studies found $\delta = 16.50$[1] in $CDCl_3$ and $\delta = 15.60$[2] CCl_4 for **1**. This large variation found for the ^1H OH chemical shifts of **1** must be due to intermolecular exchange or to divergence in solvent shielding capacities.

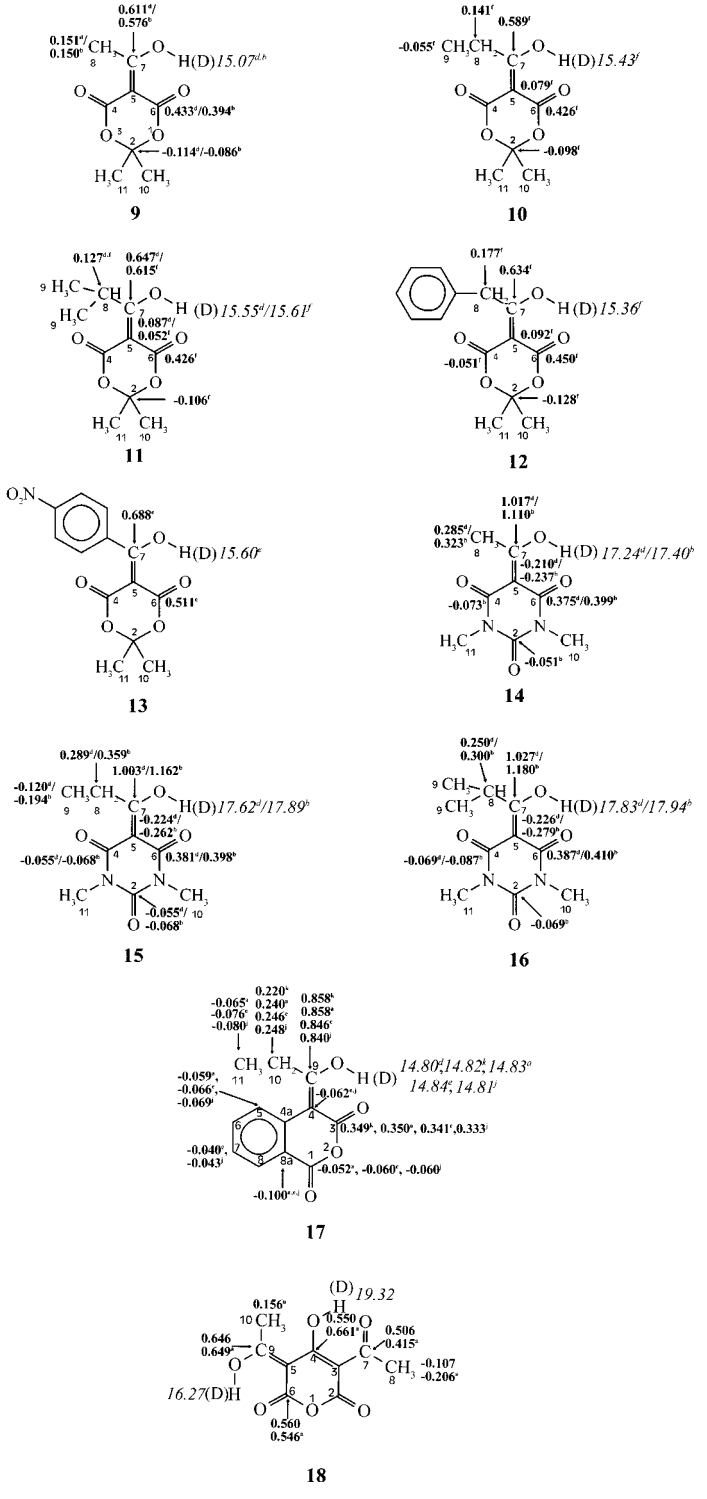
For **1** a coupling of 2.05 Hz at 190 K is observed between the aldehyde proton and the OH proton, earlier reported as 1.9 Hz at 198 K.[2]

For the enolic 2-acyl Meldrum's acids **9–13**, the enolic ^1H OH chemical shifts are found between $\delta = 15.07$ and 15.60. The OH protons seem to have a tendency to exchange, since the ^1H OH resonances are broad at 300 K. The enolic 5-acyl-1,3-dimethylbarbituric acids **14–16** display ^1H OH chemical shifts between $\delta = 17.24$ and 17.83. The ^1H OH chemical shifts found in this work agree with the findings of Duus and co-workers.[3–5] For **17** the ^1H OH resonances are broad at 300 K.

^{13}C chemical shifts. The ^{13}C NMR chemical shifts for **1–8** are given in Table 2. The ^{13}C NMR chemical shifts for **9–12**, **13** and **14–16** are given in Refs 3, 4 and 5, respectively. For **17** and **18** the ^{13}C chemical shifts are given in Refs 6 and 23, respectively.

The assignments of the ^{13}C chemical shifts were made by means of substituent effects and HETCOR[28] and COLOC[29] spectra and were compared, when possible, with previously reported assignments. For **8** the ^1H coupled ^{13}C spectrum showed a quartet centred at 198.3 ppm, which unambiguously assigned this resonance to C-6. From this spectrum the assignment of the methyl carbon is also unambiguous.

Agreement with previous assignments was found for **1** and **3**,[1] **9–12**,[3] **13**,[4] **14–16**[5] and **17**.[6]



Scheme 1—*Continued*

For **1**–**8** the ^{13}C chemical shifts of the enolic and carbonylic carbons display temperature variations comparable to those found for enolic β-diketones,[13] whereas **9**–**17** displays smaller temperature variations.

^{17}O chemical shifts. ^{17}O chemical shifts were measured for **2, 4, 7**–**10**, **15** and **16**. The ^{17}O chemical shifts were found to be δ^{17}O-1 ≈ 498, δ^{17}O-3 ≈ 243 and δ^{17}O-7 ≈ 347 ppm for **2**, δ^{17}O-1 ≈ 504, δ^{17}O-3 ≈ 234 and δ^{17}O-7 ≈ 349 ppm for **4**, δ^{17}O-2/^{17}O-4 ≈ 285 and δ^{17}O-6 ≈ 580 ppm for **7**, δ^{17}O-1 ≈ 469, δ^{17}O-3 ≈ 215 and δ^{17}O-6 ≈ 374 ppm for **8**, δ^{17}O-1 ≈ 189, δ^{17}O-3 ≈ 189, δ^{17}O-4 ≈ 344, δ^{17}O-6 ≈ 293 and δ^{17}O-7 ≈ 189 ppm for **9**, δ^{17}O-1 ≈ 188, δ^{17}O-3 ≈ 188, δ^{17}O-4 ≈ 345, δ^{17}O-6 ≈ 291 and δ^{17}O-7 ≈ 188 ppm for **10**, δ^{17}O-2 ≈ 290, δ^{17}O-4 ≈ 342, δ^{17}O-6 ≈ 212 and δ^{17}O-7 ≈ 256 ppm for **15** and δ^{17}O-2 ≈ 290, δ^{17}O-4 ≈ 346, δ^{17}O-6 ≈ 209 and δ^{17}O-7 ≈ 257 ppm for **16**.

The assignments of **9**, **10** and **15**, **16** are based on the ^{17}O chemical shifts of Meldrum's acid and barbituric acid, respectively. The ^{17}O chemical shifts for Meldrum's acid were found to be 212 ppm for O-1/O-3

Table 1. Temperature variations on ^{1}H OH chemical shifts and on the deuterium isotope effect on ^{13}C chemical shift and the sum of two- and the four-bond deuterium isotope effects on ^{13}C chemical shift, Δ_{sum}

Compound	$\Delta_{temp}\,\delta OH$[a]	$\Delta_{temp}\,\Delta C_{enolic}$[a h]	$\Delta_{temp}\,\Delta C_{carbonylic}$[a h]	Δ_{sum}[o]	Δ_{sum}[n]
1	−2.60[b]	−3.80[b]	—	1.137[c]	—
2	−5.63[d]	−4.10[d]	2.29[d]	1.564[e]	1.419
3	−3.75[d]	−4.28[d]	2.11[d]	1.633[e]	1.460
4	−4.57[f]	−4.10[f]	2.09[f]	1.628[g]	1.487
5	−6.00[f]	−3.20[f]	1.54[f]	1.574[g]	1.460
6	−5.71[f]	−2.97[f]	0.87[f]	1.633[g]	1.486
7	−1.43[f]	−2.40[f]	−2.40[f]	2.288[g]	1.952
8	—	−6.70[i]	—[j]	1.005[k]	—
9	0.00[l]	0.35[l]	−0.39[l]	0.970[m]	1.044
11	−0.86[f]	—	−0.46[f]	1.041[g]	—
10	—	—	—	1.015[g]	—
12	—	—	—	1.084[g]	—
13	—	—	—	1.199[e]	—
14	−1.60[l]	−0.93[l]	−0.24[l]	1.509[m]	1.393
15	−2.70[l]	−1.59[l]	−0.017[l]	1.543[m]	1.401
16	−1.10[l]	−1.53[l]	−0.23[l]	1.590[m]	1.414

[a] 10^{-3} ppm K^{-1}.
[b] 200–300 K.
[c] 200 K.
[d] 200–300 K.
[e] 220 K.
[f] 230–300 K.
[g] 230 K.
[h] Enolic and carbonylic refer to the carbon most on the enolic and carbonylic form, respectively.
[i] 170–190 K.
[j] No isotope effect is observed at 190 K.
[k] 170 K.
[l] 200–300 K.
[m] 200 K.
[n] 300 K.
[o] At low temperature.

Table 2. ^{13}C chemical shifts (ppm) of compounds **1–8**, obtained at 300 K, 0.5 M in $CDCl_3$ and at low temperature in CD_2Cl_2

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11
1	195.1	113.4	195.1	45.4	50.9	32.0	190.9	—	—	28.4	28.4
	196.0[a]	112.9[a]	194.9[a]	44.4[a]	50.4[a]	32.3[a]	192.6[a]	—	—	28.3[a,b]	28.3[a,b]
2	195.3	113.5	198.7	33.3	19.1	38.6	203.0	28.7	—	—	—
	196.3[c]	113.1[c]	199.2[c]	33.0[c]	18.8[c]	38.5[c]	203.8[c]	30.4[c]	—	—	—
3	195.0	112.5	198.0	46.9	52.5	30.7	202.6	28.4	—	28.0	28.0
	195.5[d]	112.3[d]	198.3[d]	46.3[d]	52.2[d]	30.9[d]	203.2[d]	29.4[d]	—	28.0[d]	28.0[d]
4	195.0	111.8	197.1	46.6	52.5	30.6	206.3	34.0	8.3	28.1	28.1
	195.4[e]	111.4[e]	196.9[e]	45.8[e]	52.0[e]	30.6[e]	206.5[e]	34.4[e]	7.7[e]	27.8[e]	27.8[e]
5	194.8	111.0	198.6	47.0	52.9	30.5	209.8	36.0	18.7	28.1	28.1
	195.2[e]	110.4[e]	198.5[e]	46.4[e]	52.3[e]	30.5[e]	209.9[e]	36.0[e]	18.5[e]	27.9[e]	27.9[e]
6	195.1	113.2	197.8	47.0	52.8	30.4	204.5	48.6	28.1	28.2	28.2
	195.7[e]	112.8[e]	198.3[e]	46.6[e]	52.5[e]	30.6[e]	204.8[e]	48.1[e]	28.0[e]	28.2[e]	28.2[e]
7	24.3	192.6	119.0	192.6	24.3	200.4	31.9	—	—	—	—
	25.5[e]	193.8[e]	118.8[e]	193.8[e]	25.5[e]	201.7[e]	33.0[e]	—	—	—	—
8	199.9	114.6	203.6	28.4	33.7	198.3	25.8	—	—	—	—
	201.5[f]	115.2[f]	203.5[f]	28.2[f]	33.9[f]	200.0[f]	27.6[f]	—	—	—	—

For assignment of carbon atoms, see Scheme 1.
[a] 200 K.
[b] Broad.
[c] 210 K.
[d] 220 K.
[e] 230 K.
[f] 190 K.

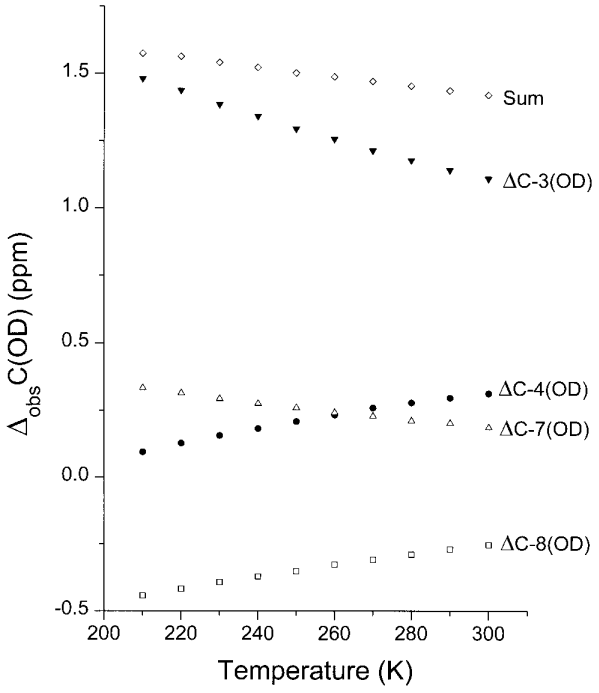


Figure 2. Deuterium isotope effects on ^{13}C chemical shifts for **2** as a function of temperature. The sum is that of ΔC-3(OD) + ΔC-7(OD).

and 376 ppm for O-4/O-6 and for barbituric acid 312 ppm for O-2 and 391 ppm for O-4/O-6.

Isotope effects

The deuterium isotope effects on ^{13}C chemical shifts are given in Scheme 1. For **2** the isotope effects of C-3, C-4, C-7, C-8 and the sum of ΔC-3(OD) and ΔC-7(OD) are given in Fig. 2 as a function of temperature. The significant temperature variations seen for **2** are also observed for **1** and **3–8**. Compounds **9**, **11** and **17** show a decreasing isotope effect on both the carbonylic C-6 (C-3 for **17**) and the enolic C-7 (C-9 for **17**) with decreasing temperature. For **9** a temperature dependence of the deuterium isotope effects is also observed on C-2, but not on C-8. For **9**, **11** and **17** the temperature variations are only one tenth of those observed for **1–8** (Table 1). For the enolic 5-acyl-1,3-dimethylbarbituric acids **14–16**, an increase in the isotope effects is observed for C-8, the enolic C-7 and the carbonylic C-6, whereas the isotope effect on C-5 decrease with decreasing temperature. The effects of temperature variations on the deuterium isotope effects for **14–16** are in the region between those observed for the β-triketones **1–8** and Meldrum's acids **9–13**.

The isotope effects on the ^{13}C chemical shielding are large for all the compounds studied, and the effects are observed throughout the system. For **9–16** unusual isotope effects are observed on C-2. C-2 is positioned after the ester oxygen or the amide nitrogen for Meldrum's and barbituric acids, respectively.

The OH proton show a tendency for intermolecular exchange for **1**, **8**, **10–13** and **17**, and therefore isotope effects are not observed at 300 K. For **8** the isotope effects were only observed when the sample was cooled to 190 K. This was also seen for 2-acyl-1,3-indandiones.[1,18]

For **1–8** the isotope effects on C-4 (C-1/C-5 for **7**) and the enolic carbon C-3 (C-2/C-4 for **7**) increase with decreasing temperature. For C-8 and the carbonylic carbon C-7 a decrease in the deuterium isotope effects is observed with decreasing temperature (for **2–6**).

For the C-9 methyl carbon of **15**, isotope effects of −0.120 ppm at 300 K and −0.194 ppm at 200 K are observed. This is a large four-bond isotope effect compared with, e.g., what is found for 2-propionyl-1,3-indandione.[18]

ΔH(OD). A deuterium isotope effect of 0.045 ppm on the aldehyde proton is observed for **1** at 170–220 K (Scheme 1).

For **2** an isotope effect on the methyl protons with a magnitude of 0.007 ppm is observed in the range 200–300 K (Scheme 1).

DISCUSSION

^{1}H OH chemical shifts

The ^{1}H OH chemical shifts for the compounds studied appear at high frequency, indicating general strong intramolecular hydrogen bonding.[24] When the temperature is lowered the ^{1}H OH chemical shift moves to higher frequency. For the barbituric acids (**14–16**) there is an increase in the ^{1}H OH chemical shift as the alkyl group of the 5-acyl moiety increases in size. This is due to steric compression as observed for the 2-acyl-1,3-indandiones.[18]

A ^{1}H OH chemical shift of 14.87 ppm is observed for **8**, with a five-membered ring system. This value is significantly smaller than the values found for the six-membered and open systems, **2–7**. This is due to the less favourable hydrogen bonding geometry in the five-membered ring system. The ^{1}H OH chemical shifts found for **1–8** are at significantly higher frequency than those found for the corresponding enolic β-diketones.[13,21,30,31]. The difference is of the order of 2–3 ppm, which indicates that the carbonyl group not involved in hydrogen bonding contributes to the resonance, as shown in forms C and D in Fig. 3. A similar high-frequency ^{1}H OH chemical shift is also seen for other enolic β-diketones with a carbonyl in the α-position.[2,31] Compounds **9–13** are esters and should therefore be compared with enolic β-keto esters such as ethyl acetoacetate (^{1}H OH chemical shift found at 12.11 ppm).[32] The difference of *ca.* 3 ppm between the ^{1}H OH chemical shift of enolic 5-acyl Meldrum's acids and those of the enolic β-keto esters can also be explained by the resonance contributions of forms C and D in Fig. 3. For **17** a difference of *ca.* 2.5 ppm is observed, which can be explained by the conjugative influence of the

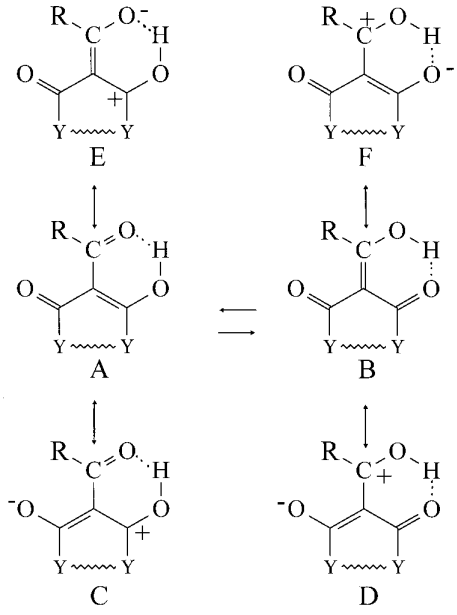


Figure 3. Resonance forms of 2-acyl-1,3-cycloalkanediones (Y = C), 5-acyl Meldrum's acids (Y = O) and 5-acylbarbituric acids (Y = N).

phenyl ring, in a way similar to 3-phenylpentane-2,4-dione ($\delta OH = 16.8$) compared with pentane-2,4-dione ($\delta OH = 15.4$).[31]

^{13}C chemical shifts

For **2–8** the two carbonyl carbon resonances and that of the enolic carbon are constantly observed above 195 ppm. These high-frequency chemical shifts are partly explained by the intramolecular enol–enol tautomeric equilibrium.[2] The C-3 and C-7 chemical shifts for **2** (198.7 and 203.0 ppm) are seen to be deshielded when compared with the carbonylic/enolic carbon chemical shifts of acetylacetone (191.2 ppm).[1,13] This deshielding agrees with the general finding for the O=C—C=C fragment,[33] implying that the resonance forms C and D in Fig. 3 are contributing.

To extend this comparison further, the averaged C-2/C-4 chemical shift of **7** is found at 192.6 ppm, which is much lower that those for C-3 and C-7 of **2** (Table 2). For **7** the chemical shift of C-6 is at 200.4 ppm, which upon comparison with that of 195.3 ppm for C-1 of **2** indicates that the acetyl group of **7**, is less strongly involved in conjugation than the free carbonyl group of **2**.

^{17}O chemical shifts

The ^{17}O chemical shifts for **7** show that the resonance for the α-acetyl group (580 ppm) is very close to the value found for simple methyl alkyl ketones.[34] This shows that the α-acetyl group of **7** is not conjugatively interacting to any large extent with the rest of the molecule.

For **2**, **4** and **8** the picture is different. The resonances of the oxygen at C-1 are now at 498 ppm for **2**, 504 ppm for **4** and at 469 ppm for **8**, considerably to lower frequency than oxygens of the C=O groups of cyclohexanone and cyclopentanone.[35] For **8** ^{17}O-6 is at higher frequency than ^{17}O-7 for **2** and ^{17}O-3 is to lower frequency for **8** than for **2**, which supports the idea that **8** is more represented by form A (Fig. 3) than **2** (see later). The sum of δ^{17}O-3 and δ^{17}O-7 for **2** is *ca.* 590 ppm and for **8** the sum of δ^{17}O-3 and δ^{17}O-6 is *ca.* 589 ppm, which is a high frequency shift of 60–70 ppm compared with the sum found for 2-acetylcyclohexanone and 2-acetylcyclopentanone.[36] Assuming that the CH_3C=O oxygen of the C-3, C-2, C-7 system is unperturbed by the C=O group at C-1 and using the mole fraction (0.6 for **2** and **4** and 0.65 for **8**) and the estimated ^{17}O chemical shifts for the carbonyl form, (acetyl $\delta^{17}O \approx 426$ ppm and propionyl $\delta^{17}O \approx 419$ ppm)[13] leads to δC-7^{17}OH ≈ 228 ppm for **2**, δC-7^{17}OH ≈ 244 ppm for **4** and δC-6^{17}OH ≈ 277 ppm for **8**. These results support the conclusion reached previously: the =CHOH oxygen is shifted considerably to higher frequency compared with β-diketones,[13] again underlining the positive charge at oxygen. These high frequency shifts shows that the use of standard values as presented by Gorodetsky *et al.*[36] is valid only for a group of very similar compounds.

Isotope effects

The large isotope effects on C-1, C-4, C-8, the enolic C-3 and the carbonylic C-7 for **1–6** (Scheme 1) leave little doubt that these compounds display intramolecular enol–enol tautomerism, in agreement with earlier findings.[2] The isotope effects at C-3 and C-7 consist of intrinsic and to a large extent of equilibrium shift contributions. Assuming that the acetylic carbonyl carbon chemical shift is to higher frequency than the corresponding enolic carbon chemical shift, and that the carbonyl carbon chemical shift of C-3 is to higher frequency than the enolic carbon chemical shift, then the relatively small isotope effect at C-7 and the large positive isotope effect at C-3 indicate that the equilibrium is shifted in the direction of the tautomer shown in Scheme 1. This is most likely also the dominant tautomer, judging from the large isotope effects found on C-3 as the equilibrium upon deuteration normally leads to more of the most stable tautomer.[13,17] This finding is corroborated by the ^{13}C chemical shifts (see above).

Only small changes are observed in the isotope effects on changing the acyl group from acetyl (**2** and **3**) to pivaloyl (**6**), which indicates that no steric hindrance is at play, although this might have been expected[37] (see later).

Compound **8** is seen to exhibit intramolecular enol–enol tautomerism from a comparison of the isotope effects on the enolic C-3 and the carbonylic C-6 carbons (Scheme 1), with the corresponding isotope effects for the enolic and carbonylic carbons of tautomeric 2-

acetylcyclopentanone (0.949 and −0.125 ppm, respectively[13]). This is further supported by the large isotope effects found for C-4 and the large negative value also found for C-7, and in agreement with earlier reports.[2] The five-membered ring structure offers a less favourable hydrogen bond, and therefore smaller isotope effects can be expected for **8**, compared with **2**. Judging from the isotope effect on C-3, it is clear that the C-3 enolic form [see Fig. 3(A)], must be dominating (see above). This is unusual, since the five-membered ring system normally prefers the tautomer with the exocyclic double bond [Fig. 3(B)].[13,30]

The isotope effects found for C-7 in **9–13** show that this carbon is enolic (form B in Fig. 3). To establish the occurrence of enol–enol tautomerism for **9–13** is not a trivial task. If the isotope effects were to be interpreted as if **9–13** were non-tautomeric, for the C-7 enolic forms we would have a $^{2}\Delta$C-7(OD) value of *ca.* 0.6 ppm, which is a large two-bond isotope effect never observed in esters but only for ketones.[1,18] The isotope effect on C-3 would then be a four-bond isotope effect, and a four-bond isotope of 0.4–0.5 ppm has never been observed in non-tautomeric systems. The isotope effects on C-2, a six-bond effect of the order of −0.1 ppm, observed for **9**, **10** and **11**, are also very unusual, owing to the ester oxygen between the site of exchange and the carbon in question. This type of isotope effect is not seen for esters. If **9–13** were non-tautomeric and only on the C-7 enolic form, we would expect, based on isotope effect measurements of the enol form of β-keto esters,[13,15] the following intrinsic isotope effects: C-7 ≈ 0.4, C-6 ≈ 0.1 and C-8 ≈ 0.1 ppm, and little else. The observed isotope effects of **9–13** do not fit this picture unless a tautomeric equilibrium is at hand.

In order further to prove the presence of a tautomeric equilibrium, the temperature dependence on the isotope effects was measured. For **9** and **11** a decrease with decreasing temperature for both ΔC-6 and ΔC-7 is seen (Table 1). This is unusual because normally they would be in the opposite direction. It is seen that both isotope effects at C-6 and C-7 are larger than their intrinsic contributions, meaning that both equilibrium contributions are positive. This is unusual, but can be explained, as seen below, if the chemical shift of both nuclei is to higher frequency in one tautomer than in the other. For **9** the isotope effects and the changes in chemical shifts with temperature both support the contention that the structure shown in Scheme 1 is dominant. Assuming that $\delta(^{13}CH_3CO) > \delta(^{13}CH_3COH)$ and that $\delta[=^{13}C(OH)—O] > \delta(^{13}COO)$ the change in chemical shifts will be positive upon lowering of the temperature. Upon deuteration the equilibrium contributions for both C-6 and C-7 will be positive and of approximately the same magnitude, judging from the changes observed with changes in temperature (Table 1). C-6 will have a small intrinsic contribution as the C-6 enolic form is only slightly populated. C-7 will have a relatively small intrinsic contribution as $^{2}\Delta$C(OD) for an enolic β-keto-ester is *ca.* 0.4 ppm.[13,15] A rough estimate suggests that the form shown in Scheme 1 contributes around 80%.

The isotope effect on C-7 for **14–16** shows that C-7 are on the enolic form (form B in Fig. 3). The large isotope effects on C-5, C-8, the carbonylic C-6 and the enolic C-7 clearly demonstrate that the 2-acyl-1,3-dimethylbarbituric acids are tautomeric. For **15** isotope effects of −0.12 ppm at 300 K and −0.194 ppm at 200 K are observed at C-9. Such effects are not observed in an aliphatic moiety four bonds away from the site of deuteration unless the system is tautomeric (see **4**).[13] The isotope effect on C-2 is unusual owing to the amide nitrogen between the site of deuteration and the carbon in question. This type of effect is only observed in tautomeric systems.[17] The temperature dependence on the isotope effects for **14–16** are negative for both C-6 and C-7 (Table 1), as was observed for the enol form of β-ketoamides.[16]

Sum of the isotope effects on the carbonylic and enolic carbon, Δ_{sum}

Δ_{sum} is equal to ΔC-3 + ΔC-7 for **1–6**, ΔC-2 + ΔC-4 for **7**, ΔC-3 + ΔC-6 for **8**, ΔC-6 + ΔC-7 for **9–16**, ΔC-3 + ΔC-9 for **17** and ΔC-6 + ΔC-9/ΔC-4 + ΔC-7 for **18**. The ^{1}H OH chemical shifts increase as the sum of the observed two- and four-bond isotope effects increase (Fig. 4) Figure 4 shows that the tautomeric compounds have a larger sum compared with localized hydrogen-bonded compounds for the same ^{1}H OH chemical shifts. In Fig. 4 the compounds having a localized hydrogen bond are represented by *o*-hydroxyacyl-aromatic and 2-acyl-1,3-indandiones.[1,18] The enolic triketones and the 5-acylbarbituric acids are seen to have a higher ^{1}H OH chemical shift than the enolic β-diketones having the same Δ_{sum}. Exceptions from this are **7** and enolic ethyl 2-acetyl-3-oxobutyrate,[38] both of which have an unusually high Δ_{sum} (Fig. 4).

For tautomeric enolic β-diketones two rules of thumb have been established. For six-membered rings the sum of the isotope effect on the enolic and carbonylic carbons, Δ_{sum}, are above 1.2 ppm, and for a five-membered ring system above 0.8 ppm.[13] Δ_{sum} for **2–6** are above 1.2 ppm and for the five-membered **8** above 0.8 ppm, which again reveal that these compounds display tautomerism.

The Δ_{sum} for **9–13** are between 0.970 and 1.199 ppm. The carbonylic carbons of these compounds are part of an ester moiety. Esters normally display smaller isotope effects than ketones.[13,25,39,40] The Δ_{sum} for ethyl acetylacetate which forms a localized hydrogen bond is 0.54 ppm.[15] The Δ_{sum} for **9–13** indicate that these display tautomerism. The Δ_{sum} for **17** is 1.208 ppm and for **18** 1.206 ppm[17] for C-6/C-9. C-6 is an anhydride carbonyl carbon acting as an acceptor. The Δ_{sum} for **17** and **18** further prove that these compounds display tautomerism.[6,9,17,23]

The Δ_{sum} for **14–16** are between 1.38 and 1.41 ppm. For tautomeric enolic β-ketonamides the Δ_{sum} are between 1.11 and 1.48 ppm.[16] The large Δ_{sum} observed for **14–16** indicate that they are tautomeric.

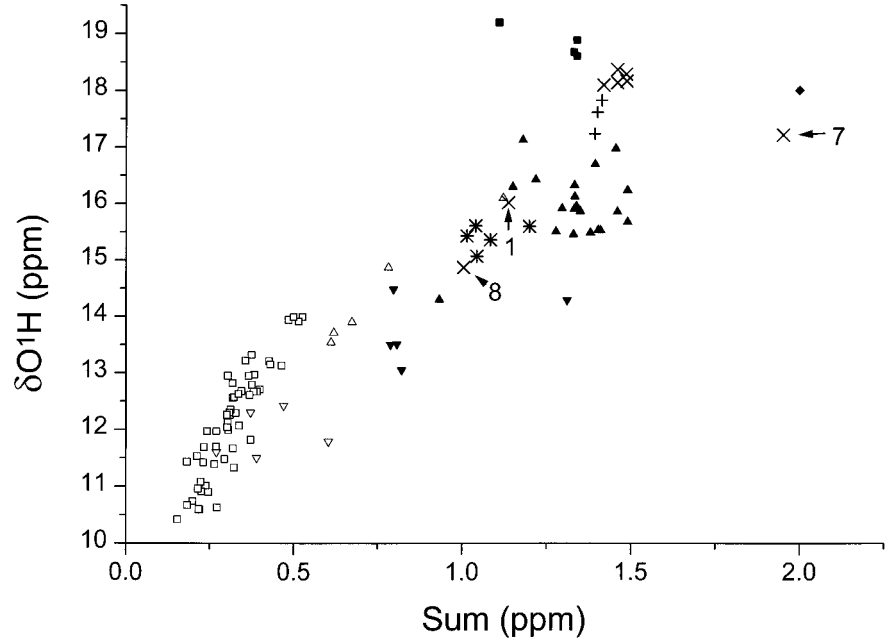


Figure 4. Plot of the ^{1}H OH chemical shifts (in ppm) as a function of the sum of the isotope effects on the enolic (or hydroxy for non-tautomeric compounds) carbon and the carbonylic carbon. Open symbols indicate compounds which are considered having a localized hydrogen bond and solid symbols indicate compounds which are considered to display enol–enol tautomerism. □, 2-Hydroxyacyl-aromatic compounds (from Ref. 25); ▲, open-chain and six-membered ring enolic β-diketones (from Refs 13 and 15); ▼, enolic five-membered ring β-diketones (from Ref. 13); △, enolic 2-acyl-1,3-indanediones (from Refs 1 and 18); ■, usnic acid and its derivatives (from Ref. 15); ◆, enolic ethyl 2-acetyl-3-oxobutyrate (from Ref. 40); ▽, enolic five-membered ring β-diketones. ×, Compounds **1–8**; +, compound **14–16**; ∗, compounds **9–13**.

Equilibrium constant, K_{eq}

The equilibrium constant describing the intramolecular enol–enol interconversion is $K_{eq} = [A]/[B] = x/(1 - x)$, [A] and [B] being the concentrations of forms A and B in Fig. 1 and x the mole fraction of form A.

We have reported earlier[13] the isotope effects on the enolic and carbonylic carbons for enolic β-diketones as a function of the molar fraction, x. The part for $x = 0$–0.5 is based on five-membered ring systems and the part for $x = 0.5$–1 on six-membered ring systems. For the five-membered ring system the picture between $x = 0.5$–1.0 is expected to be a reflection around $x = 0.5$ of $x = 0$–0.5. For the six-membered system a reflection around $x = 0.5$ of $x = 0.5$–1.0 is expected for $x = 0$–0.5. This gives the function shown in Fig. 5, where the solid line is the polynomial fit to the data in Ref. 13 and the dotted lines are the reflected part. The isotope effects on the enolic and carbonylic carbons give two fixed points that will be concurrent with four different mole fractions. From the isotope effects on the enolic and carbonylic carbons the $x < 0.5$ and $x > 0.5$ situations can be distinguished, leaving two different mole fractions. From the effect of temperature variations on the isotope effects, these two situations can be further distinguished. For **2** ΔC-7 is 0.310 ppm and ΔC-3 is 1.109 ppm at 300 K, which is concurrent to $x \approx 0.04$–0.06, 0.41, 0.58 or 0.93–0.96 (see guidelines in Fig. 5). The largest isotope effect is on C-3 which means that the tautomeric equilibrium can be located above $x = 0.5$. With decreasing temperature the population is shifted in favour of the most populated enol form at ambient temperature. The increase in the isotope effect on C-3 and the decrease in the isotope effect on C-7 at 220 K strongly point towards a mole fraction of 0.58. From analogy with the above description, the mole fractions for **3–6** were found to be 0.58–0.60 and for **8** 0.60. Compound **7** is a symmetric molecule. The mole fraction for **1** is determined to be 0.65–0.70 and that for **14–16** to be 0.45. The model is based on an enolic β-diketone, and **1** being an aldehyde and **14–16** being amides make the determination of the mole fractions tentative. Using the observed ^{17}O chemical shifts for the acyl group and the estimated separate ^{17}O chemical shifts,[13] the mole fractions are estimated to be 0.74 for **2**, 0.77 for **4**, 0.82 for **8**, 0.46 for **15** and 0.47 for **16**. Owing to the conjugations with the non-hydrogen bonded carbonyl [Fig. 3(D)], the measured ^{17}O chemical shift is higher than in a non-conjugated acyl group. This means that the mole fraction estimated from ^{17}O chemical shifts is too high.

The mole fractions for **9–13** cannot be determined from deuterium isotope effects on ^{13}C chemical shifts as these are smaller for esters. From the ^{17}O-7 chemical shifts the mole fraction is determined to be 0.24 for **9** and 0.23 for **10**. For **17** the δ^{17}O-9 of 167 ppm[6] can be converted to a mole fraction of 0.16 by using the estimated separate ^{17}O chemical shifts.[13] Owing to the conjugations with the carbonyl group for **9** and **10** and the phenyl ring for **17**, the measured ^{17}O chemical shifts is higher than in a non-conjugated acyl group. This

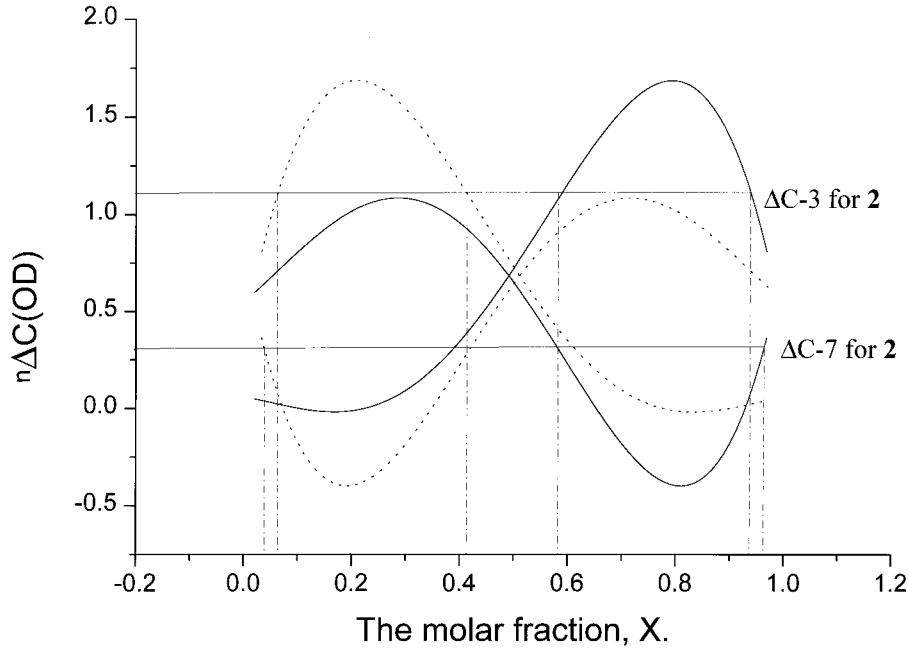


Figure 5. Observed isotope effects on the enolic and carbonylic carbon as a function of the mole fraction *x*. The solid line is a fourth-order polynomial fit to the observed data from Ref. 13. The dotted line is the reflection of the solid line around $x = 0.5$.

means that the mole fractions estimated for the ^{17}O chemical shifts are the upper limit.

CONCLUSIONS

The enolic 2-acyl-1,3-cycloalkanediones, 5-acyl Meldrum's acids and 5-acyl-1,3-dimethylbarbituric acids studied have been found to exhibit intramolecular enol–enol tautomerism using isotope effects on ^{13}C nuclear shielding. The equilibrium constants are estimated from the deuterium isotope effects on the enolic and carbonylic carbons. The equilibrium constants are found to be 1.5 for the enolic 2-acyl-1,3-cyclohexanediones and 2-acetyl-1,3-cyclopentanedione in favour of the form having an endocyclic double bond. For 5-acyl-1,3-dimethylbarbituric acids an equilibrium constant of 0.8 is found, favouring the exocyclic enolic form. The equilibrium position is not much affected by variation of the acyl group. Changes in isotope effects due to steric hindrance were not observed for 2-pivaloyl-1,3-cyclohexanedione compared with 2-acetyl-, 2-propionyl- and 2-isobutyryl-1,3-chclohexanedione. An increase in the ^{1}H OH chemical shift due to steric compression is observed for 5-acyl-1,3-dimethylbarbituric acids on changing the 5-acyl group from acetyl to isobutyryl.

The ^{17}O, ^{13}C and ^{1}H chemical shifts show that the resonance forms, in which the α-carbonyl is negatively charged, are important.

EXPERIMENTAL

Compounds

2-Acetyl-1,3-cyclohexanedione (**2**), triacetylmethane (**7**), 2-acetyl-1,3-cyclopentanedione (**8**) and 3,5-diacetyltetrahydropyran-2,4,6-trione (**18**), were purchased from Aldrich. 2-Formyl-4,4-dimethyl-1,3-cyclohexanedione (**1**), 2-propionyl-4,4-dimethyl-1,3-cyclohexanedione (**4**) and 2-isobutyryl-4,4-dimethyl-1,3-cyclohexanedione (**5**) were prepared according to Ref. 41. 2-Acetyl-4,4-dimethyl-1,3-cyclohexanedione (**3**) and 2-pivaloyl-4,4-dimethyl-1,3-cyclohexanedione (**6**) were prepared analogously to **4** using anhydrous sodium acetate–acetic anhydride and anhydrous sodium pivalate–pivalic anhydride, instead of anhydrous sodium propionate–propionic anhydride.

5-(1-Hydroxyethylidene)-2,2-dimethyl-4,6-dioxo-1,3-dioxane (**9**), 5-(1-hydroxypropylidene)-2,2-dimethyl-4,6-dioxo-1,3-dioxane (**10**), 5-(1-hydroxy-2-methylpropylidene)-2,2-dimethyl-4,6-dioxo-1,3-dioxane (**11**), 5-(1-hydroxy-2-phenylethylidene)-2,2-dimethyl-4,6-di-oxo-1,3-dioxane (**12**), 5-(1-hydroxy-4-nitrobenzylidene)-2,2-dimethyl-4,6-dioxo-1,3-dioxane (**13**), 5-(1-hydroxyethylidene)-1,3-dimethyl-2,4,6-trioxo-1,3-diazane (**14**), 5-(1-hydroxypropylidene)-1,3-dimethyl-2,4,6-trioxo-1,3-diazane (**15**) and 5-(1-hydroxy-2-methyl-propylidene)-1,3-dimethyl-2,4,6-trioxo-1,3-diazane (**16**) were prepared as described in Refs 3–5. 4-Propionylisochroman-1,3-dione (**17**) was prepared as described in Ref. 6.

NMR experiments

The ^{13}C NMR spectra were recorded in CD_2Cl_2 or $CDCl_3$ on a Bruker AC 250 NMR spectrometer at 62.89 MHz with a digital resolution of 0.55 Hz per point. Spectra of samples with different degrees of deuterium incorporation were measured to determine the signs of the isotope effects. The ^{13}C chemical shifts were measured relative to internal TMS at 0.5 M in $CDCl_3$ at 300 K and in CD_2Cl_2 at 170–230 K with a digital

resolution of 1.1 Hz per point. The ^{17}O chemical shifts (natural abundance) were measured relative to external $H_2\,^{17}O$ at 3 M in $CDCl_3$ at 300 K, with a digital resolution of 34.9 Hz per point at 33.908 MHz. Typically 2×10^5–6×10^5 scans were accumulated.

HETCOR[28] and COLOC[29] spectra were recorded as described in Ref. 40.

Deuteration of compounds

Amounts of 100 mg of liquid compounds were dissolved in 1 ml of CD_2Cl_2 and stirred with 0.5 ml of D_2O–H_2O, usually overnight. The D_2O–H_2O phase was removed and the remaining organic phase was dried over anhydrous Na_2SO_4. Crystalline compounds were dissolved in MeOD–MeOH and evaporated. The degree of deuteriation was varied by varying the MeOD:MeOH or D_2O:H_2O ratios, and it was estimated from the ^1H NMR spectra.

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