JOURNAL OF PHYSICAL ORGANIC CHEMISTRY, VOL. 4, 225–232 (1991)

LONG-RANGE DEUTERIUM ISOTOPE EFFECTS IN TAUTOMERIC β-THIOXOKETONES. A ^{1}H AND ^{13}C NMR STUDY

POUL ERIK HANSEN,* ULRIK SKIBSTED AND FRITZ DUUS

Institute of Life Sciences and Chemistry, Roskilde University, P.O. Box 260, DK-4000 Roskilde, Denmark

Equilibrium displacements within the enol–enthiolic tautomeric systems of β-thioxoketones caused by long-range isotope effects were monitored by ^{1}H and ^{13}C NMR spectroscopy. Thioacetylacetone and 1,3-diphenyl-3-thioxopropanone deuteriated at various positions were investigated. Both compounds are in fast (*Z*)-enol–(*Z*)-enethiol equilibrium on the NMR time scale. The investigations showed that CD_3 and C_6D_5 groups changes the equilibrium so that the tautomer having a C=X bond next to the CD_3 or C_6D_5 groups decreases. Deuteriation at the methine position pushes the equilibrium towards the (*Z*)-enol form. The study further showed that deuteriation at the phenyl ring next to the C=O group causes the largest effect if the deuterium is at the *ortho* position and the smallest if it is at the *para* position. Long-range effects on equilibrium are discussed in general in order to establish a common pattern. Deuterium scrambling is observed both during the coupling reaction of ethyl thionoacetate with hexadeuterioacetone and during preparation of specifically labelled acetophenone. The latter compounds are synthesized by acetylation of specifically labelled benzenes. The scrambling reaction is suggested to be a transdeuteriation of the deuteriated benzenes rather than involving the acetophenones.

INTRODUCTION

Isotopic substitution may cause changes in reaction rates,[1,2] in the position of equilibria[1,2] and nuclear shielding.[3–5] The common cause of these effects is the change in the vibrational frequencies and the lowering of the zero-point energy.[1] Kinetic isotope effects caused by isotopic substitution far away from the nuclear reaction centre are usually very difficult to measure[1] and comparatively few investigations of this type have appeared.[6] Other methods leading to deuterium isotope effects are therefore useful, and the application of deuterium isotope effects on chemical shifts is such a method. These are defined as $^{n}\Delta X(D) = \delta X(H) - \delta X(D)$, X being either ^{1}H or ^{13}C and *n* the number of bonds between the site of deuteriation and the nucleus in question. They may be of two types, intrinsic (direct) or equilibrium isotope effects, and the latter type were considered in this study. Equilibrium isotope effects have been investigated in a series of tautomeric compounds including β-diketones[7,8] and β-thioxoketones.[9] β-Thioxoketones are known to exist in solution as an equilibrium mixture of rapidly interconverting tautomeric (*Z*)-enol and (*Z*)-enethiol forms with a preponderance of the former.[10] The latter type of compound is very suitable for such studies as the difference in the ^{13}C chemical shifts of the C=S and the C–SH carbons is very large.[9]

This study covered thioacetylacetone deuteriated to varying extents at all positions, and is hence complementary to the study of acetylacetone.[7] In addition, selectively deuteriated 1,3-diphenyl-3-thioxopropane-1-one was studied. The change in the equilibrium can be measured by means of ^{13}C NMR, but also very accurately by ^{1}H NMR. The large differences in chemical shifts between C=S and C–SH carbons or between C–O*H* and C–S*H* proton chemical shifts[10] make the system very sensitive. Another advantage of these compounds is the ease with which they are synthesized[10–12] and the detailed knowledge of their structural dynamics.[10]

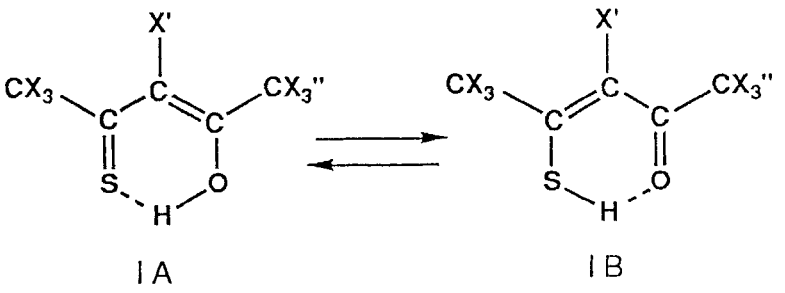
The long-range isotope effects obtained by means of NMR measurements may be compared with equilibrium isotope effects obtained by other measurements such as changes in acidity constants[13] or changes in hydrolysis rates.[2]

The inclusion of the aromatic β-thioxoketones makes it possible to approach the question whether deuteriation of the *ortho*, *meta* and *para* positions gives rise to different isotope effects. Deuteriation in *ortho*, *meta* and *para* positions of a benzene ring could lead to similar or different effects. However, no consensus has

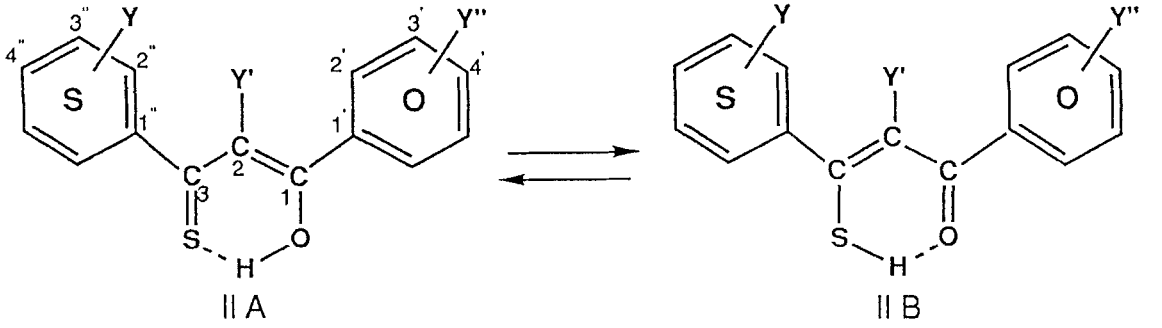
* Author for correspondence.

0894–3230/91/040225–08$05.00

Received 5 March 1990
Revised 12 December 1990



X = H or D
X' = H or D
X" = H or D



$Y = H_n D_{5-n}$; n = 0-5
$Y' = H$ or D
$Y'' = H_n D_{5-n}$; n = 0-5

Figure 1. Tautomeric equilibria of β-thioxoketones for the (*Z*)-enol–(*Z*)-enethiol forms. **I**-*S*-d_3, X = D; **I**-O-d_3, X" = D; **II**-*S*-d_5, Y = D_5; **II**-O-d_5, Y" = D_5; etc.

been reached on this point, probably owing to the different types of compounds used and the different kinds of studies undertaken. The use of both aliphatic (**I**) and aromatic (**II**) compounds (see Figure 1) in this study could probably help to clarify some of these points. In a number of instances deuterium has been treated as a substituent[6] and recently substituent parameters have been derived by measuring direct isotope effects on ^{13}C nuclear shielding.[14,15] In these studies deuteriation of any position on the benzene ring was considered to give the same effect. In this study this approach was questioned.

In the process of synthesizing specifically deuterium-labelled acetophenones by acetylation of specifically deuteriated benzene, some interesting deuterium scramblings took place. Scrambling experiments have only been attempted very briefly previously.[16] Another interesting point is the scrambling of the label in the coupling reaction of CH_3CSOEt and hexadeuterioacetone under basic conditions.

RESULTS

Synthesis

Deuteriated thioacetylacetone containing various amounts of deuterium at the methyl and methine groups (see Table 1) were synthesized from CH_3CSOEt

Table 1. Percentage deuterium distribution in acetylated deuteriobenzenes as determined by mass spectrometry

Starting material	Solvent	Number of deuteriums					
		0	1	2	3	4	5
Benzene-d_6	CS_2	< 0·1	< 0·1	0·3	0·3	5·6	93·6
Benzene-1,3,5-d_3	CS_2	1·7	9·8	30·2	42·0	13·7	2·5
Benzene-1,4,-d_2	CCl_4	8·2	30·5	46·3	12·4	2·4	0·2
Benzene-d_1	CCl_4	29·1	57·0	11·6	2·1	0·2	< 0·1

and hexadeuterioacetone. Scrambling leads to distribution of deuterium in all three hydrogen-containing parts. A combined analysis of mass and ^1H spectra led to an estimation of the deuterium content as shown:

$CH_3C{=}S$ group:
$CH_3 : CH_2D : CHD_2 : CD_3 = 6 : 12 : 21 : 17$;
$CH_3C{=}O$ group:
$CH_3 : CH_2D : CD_2H : CD_3 = 1 : 6 : 30 : 63$;
CH group: $CH : CD = 1 : 3$.

To synthesize specifically deuteriated derivatives of **II**, either specifically deuteriated benzonitriles, bromobenzenes or acetophenones are needed as starting materials. The latter are synthesized in a Friedel–Crafts reaction[17] starting with either mono-,1,4-di-,1,3,5-tri- or hexa-deuteriated benzenes. This reaction leads to a great deal of scrambling, as illustrated in Table 1. The data in Table 1 show that the label is moved not merely within a molecule, but isotopomers with more or fewer deuteriums are also formed. The use of CH_2Cl_2 as a solvent in the acetylation reaction leads to even greater scrambling than shown in Table 1. By combining data from ^1H NMR spectroscopy with the data in Table 1, we estimate the distribution given in Table 2. This estimation was possible only for the acetophenone arising from benzene-1,4-d_2.

A number of findings shown in Table 2 are remarkable: (i) the high content of non-deuteriated acetophenone; (ii) the small amount of 4-D-acetophenone, as this is formed directly on acetylation, (iii) the relatively small amounts of 2,4-D-acetophenone, as this is the second product formed directly; and (iv) the large amounts of both tri- and tetra-deuteriated material. The fact that very little ^1H incorporation takes place when acetylating hexadeuteriobenzene shows that moisture does not play a major role in the reaction.

Table 2. Distribution of the twelve isotopomers of acetophenone from acetylation of benzene-1,4-d_2

Isotopomer	Distribution (%)
d_0	8·0
d_1	o[a] 10·5, m 11·1, p 8·2
d_2	$o + m$ 28·15, $o + p$ 10·6, $m + p$ 7·2
d_3	$o + m + p$ 8·4, $o + 2m$[b] 3·6, $2o + m$ 0·9
d_4	$o + 2m + p$ 2·6, $2o + m + p$ 0·6

[a] o, m and p refer to sites of deuteriation relative to the substituent.
[b] $2m$ means deuteriation at both positions *meta* to the substituent, and similarly with $2o$.

The use of deuteriated acetophenones as starting material leads to 1,3-diphenyl-3-thioxopropan-1-one labelled at the benzene ring at the carbonyl side (O-benzene ring) (see Figure 1). Labelling the benzene ring at the thiocarbonyl side (S-benzene ring) requires either deuteriated benzonitriles or bromobenzenes as starting materials for the synthesis of the thionoesters or dithioesters, respectively. Both approaches have been used, leading to a fully deuteriated S-ring, or an S-ring monodeuteriated at the *ortho* position. No scrambling takes place in the condensation reaction with the aromatic precursors.

NMR spectroscopy

^1H NMR spectra.

The time-averaged proton resonance from the chelated proton depends on temperature and concentration and is observed at a chemical shift of 12–14 ppm. The analysis of a mixture of isotopomers of **I** is reasonably simple although the spectrum is complex, as shown in Figure 2. The isotope effects obtained can be considered as the results of a change in the chemical equilibrium since the intrinsic isotope effect over four bonds is negligible.[4] The data in Table 3 and Scheme 1 reveal that deuterium substitution in the two methyl groups of **I** have opposite and slightly different effects, but also that the effects of deuterium substitution within one methyl group are additive. Substitution at the methine proton has the largest effect per deuterium. The effect of deuteriation at the methyl group is similar to that observed for deuteriated acetylacetone.[7]

The ^1H isotope effects given for **II** in Scheme 1 are the result of the analysis of a series of spectra with varying extents of deuteriation at the O-ring. In the

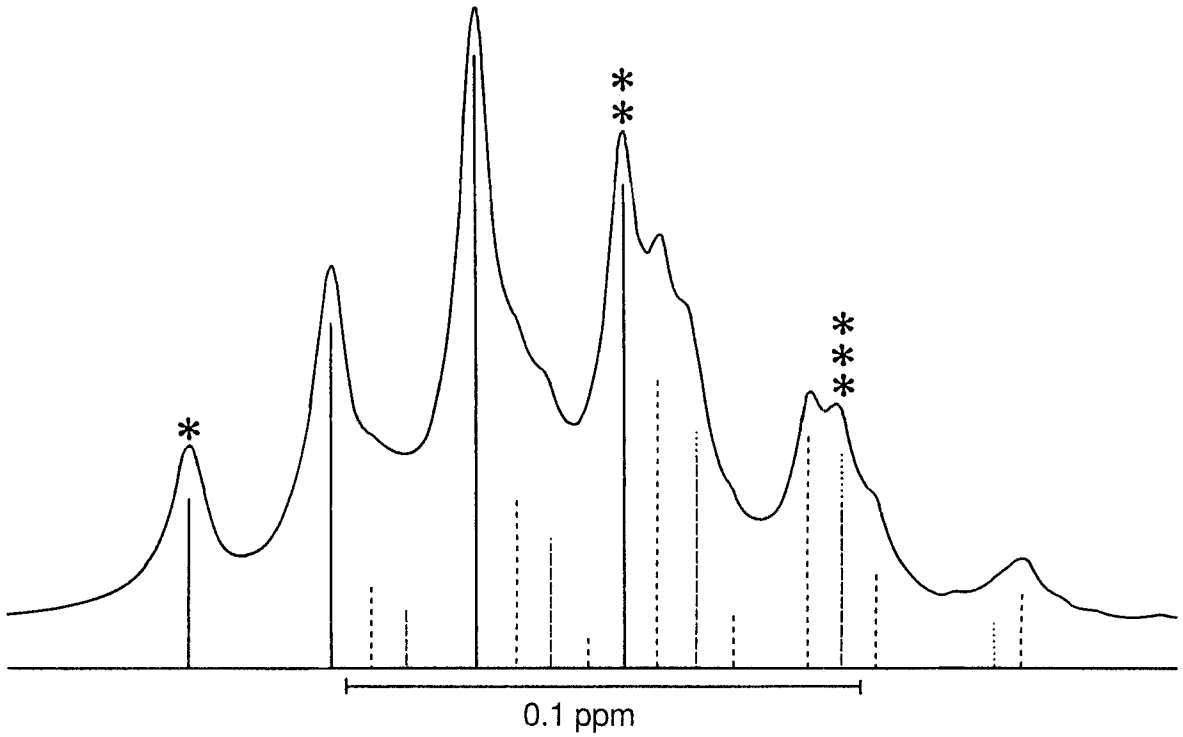


Figure 2. ^{1}H NMR spectrum of the chelate proton of deuteriated thioacetylacetone (**I**) measured at 270 MHz and 303 K. The stic diagram gives the positions and proportions of isotopomers. The peak marked * represents $CH_3CSCDCOCD_3$, ** $CD_3CSCDCOCD_3$ and *** $CD_3CSCHCOCD_3$. Solid sticks, positions of the species $CH_xD_{3-x}CSCDCOCD_3$; long dashed stick $CH_xD_{3-x}CSCHCOCD_3$; short dashed sticks, $CH_xD_{3-x}CSCDCOCHD_2$; dotted sticks, $CH_xD_{3-x}CSCDCH_2D$; x increases to the rigl

spectrum of the β-thioxoketone(s) arising from 1,4-dideuteriated benzenes, six resonances from the chelate proton could be recognized and the spectrum could be considered to consist of contributions from twelve isotopomers. Given five intensities in the mass spectrum, a set of equations could be solved and the distribution in Table 2 calculated. The results in Table 3 and Scheme 1 show clearly that the *ortho* position gives the largest effect and that the effect falls off with increasing distance. In contrast, deuteriation at the S-ring does not lead to any measurable isotope effect.

The resolution obtained in the spectra of **II** dependent on concentration. At a concentration c 2 mg ml^{-1} a good resolution is obtained, whereas poc resolution results if the concentration is increased t 70 mg ml^{-1}, as commonly used for ^{13}C NMR spectra A similar problem was not encountered with th compounds of type I.

^{13}C NMR spectra.

Deuterium isotope effects on ^{13}C chemical shifts hav

Table 3. Resonance positions of isotopomers of *O*-ring deuteriated β-diketones

Isotopomer	Resonance positions[a]							
II-*O*-d_1	3·0	7·0	—	10·4				
II-*O*-d_2	3·1	7·3	—	10·1				
II-*O*-d_1 + **II**-*O*-d_3	3·0	6·7	—	10·3	12·8	14·6	16·6	
II-*O*-d_3	3·2	6·7	7·9[b]	10·6	13·4[b]	15·0	17·0	20·7
II-*O*-d_5	—	—	—	—	—	—	21·0	

[a] Resonance position given in ppb relative to **II**-*O*-h_5.
[b] Observed as a shoulder. Position approximate.

been reported earlier, also leading to an assignment of the ^{13}C spectrum.[9] However, the specifically labelled derivatives confirm these assignments and give rise to a series of direct isotope effects in the pentadeuteriated case as seen in Scheme 1. These isotope effects clearly confirm the assignments of C-2′ vs C-3′ and those of C-2″ vs C-3″. The chemical shifts at 305 K and in dilute solution are as follows:
δ'C=S' = 202·85, δC-2 = 110·56,
δ'C=O' = 179·78 ppm, δC-1′ = 135·68,
δC-2′ = 127·12, δC-3′ = 128·73,
δC-4′ = 132·47, δC-1″ = 145·35,
δC-2″ = 126·70, δC-3″ = 128·39, and
δC-4″ = 130·95 ppm.

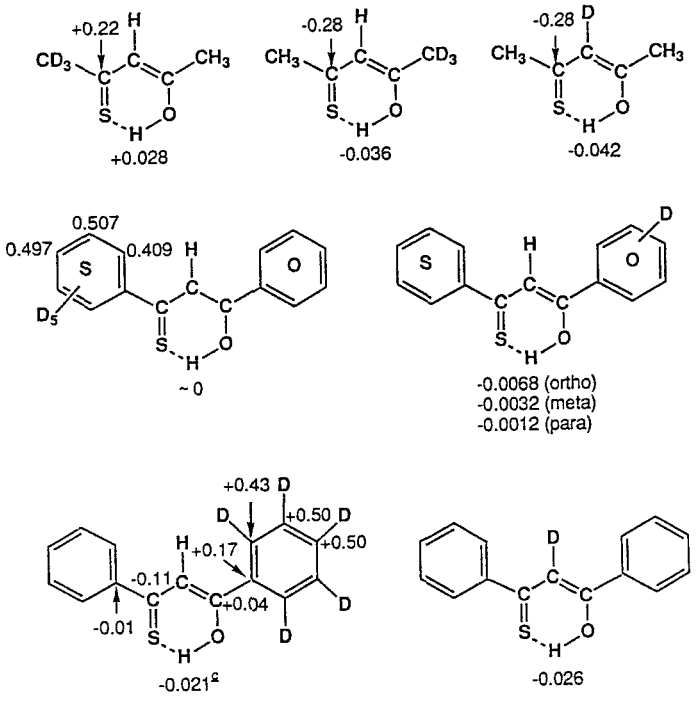
Intrinsic isotope effects.

The 'C=S' and the 'C=O' carbons of **I** may experience intrinsic isotope effects over two bonds. However, these effects are small, although not negligible, as judged from studies of keto compounds in general.[18,19]

The 'C=O' carbon or the 'C=S' carbons may likewise show small direct isotope effects over three bonds when the adjacent benzene ring in **II** is deuteriated in the *ortho* position. However, as no such effects are observed in the *o*-deuteriated acetophenones, it is considered to be negligible. Likewise, both the 'C=O' and the 'C=S' carbons may experience a direct isotope effect when Y′ = D (Figure 1). Again, judging from the effect of deuteriation at the methine carbon in acetylacetone,[20] this effect is small in the β-thioxoketones.

As the direct deuterium isotope effects are expected to be short range, the observed isotope effects at the chelate protons are clearly equilibrium isotope effects. The same holds true to a large extent for the 'C=S' and the 'C=O' carbons. These effects are given in Scheme 1.

A comparison between ^{1}H and ^{13}C data can be made if estimates of the ^{1}H and ^{13}C data for the two tautomers are known. From solvent effect studies, values of *ca* 15·8 and *ca* 2·9 ppm for the enol and the enethiol proton, respectively, in chloroform have been found.[10] The ^{13}C chemical shifts of a thiocarbonyl carbon, C=S, a C−SH, a C−OH and a carbonyl carbon, C=O, in these aromatic compounds, are estimated to be 218, 147, 175, and 198 ppm, respectively, based on deuterium isotope effects caused by deuteriation at the chelate proton.[20] A comparison of ^{1}H and ^{13}C data for **II**-*O*-d_5 and using the estimated chemical shifts for the (*Z*)-enol and (*Z*)-enethiol forms



Scheme 1. $^{n}\Delta H(D)$ and $^{n}\Delta C(D)$ isotope effects[a] in deuteriated β-thioxoketones.[b] [a]Isotope effects in ppm; defined as $^{n}\Delta X = \delta X(H) - \delta X(D)$, where X = ^{1}H or ^{13}C. Temperature 303 K. [b]Only the most populated tautomer of the β-thioxoketones is shown for brevity. [c] The magnitude depends slightly on temperature (see text)

given above, a change in the equilibrium of 0·155% using ^{13}C data and 0·163% using ^{1}H data is obtained. This supports the finding that the isotope effects are almost exclusively equilibrium effects. A comparison of deuterium substitution at the methine position shows a larger effect in **I** than in **II**.

The isotope effects observed in **I**-*O*-d_5 depends slightly on temperature. The isotope effects on the chelate proton at 300 K is 0·022 ppm, decreasing to 0·019 ppm at 250 K and to *ca* 0·015 ppm at 240 K. At the same time, the resonance for the **I**-*O*-h_5 moves from 15·193 to 15·838 ppm. The change to a lower field (higher frequency) is in accord with an increased amount of the more stable A tautomer at low temperatures. The decrease in the isotope effect is a consequence of the change in ΔG, thus confirming the equilibrium nature of the isotope effect.

A comparison of the equilibrium isotope effect observed at 'C=S' carbon in II-*O*-d_5 with that observed by deuteriation at the chelate proton ($\Delta CS = -4{\cdot}52$ ppm)[9] shows that the effects are proportional. The proportionality factor is *ca* 45.

DISCUSSION

Thioacetylacetone (**I**) exists as a tautomeric mixture, A : B = 66 : 34, in chloroform. The tautomeric equilibrium is fast on the NMR time scale and only averaged signals are observed for the 'C=S' and the 'C=O' carbons. The isotope effect observed at the 'C=S' carbon in the isotopomer **I**-*S*-d_3 at the chelate proton is to high frequency whereas the effects observed in the isotopomer **I**-*O*-d_3 are to lower frequency. This means that in **I**-*S*-d_3 the A tautomer is becoming less populated, whereas in **I**-*O*-d_3 the A tautomer becomes more populated. This is similar to findings with acetylacetone-d_3.[7] Saunders[7] rationalized this by using the rule of thumb 'that deuterium prefers to sit on the stiffer bond',[8] which means a stronger bond (a bond with a higher stretching frequency). The gain in zero-point energy is therefore larger. A C—H bond next to a carbonyl or a thiocarbonyl group will be weakened owing to resonance effect. The CD_3 group hence prefers to be next to a C—SH or a C—OH bond rather than a C=S or a C=O bond.

Another case involving a $CH_{3-x}D_xC{=}O$ situation is acetyl fluoride. Non-additivity of the deuterium isotope effects on fluorine chemical shift was found to be due to unequal rotamer distributions in the CHD_2 and CDH_2 isotopomers.[19] This is in line with the finding that the C—H bond *trans* to the C=O group has the highest stretching frequency[21] and hence prefers to be deuteriated. This, on the other hand, indicates that the two C—H bonds *gauche* to the C=O group interact most strongly. The mechanism for the deuterium effect is therefore understood in some detail. Deuteriation at the methine C—2 carbon is seen to stabilize the A form.

In II-*O*-d_5 the A form is also stabilized. In the latter case this is again equivalent to destabilizing the B form. Deuterium substitution at the phenyl ring clearly follows the same pattern as deuteriation of the methyl groups of **I**. This is understandable as a mesomeric interaction between the C—H bonds in *ortho* and *para* positions and the C=O group clearly will weaken the C—H bonds. As can been seen from Scheme 1 and Table 3, the effects caused by deuteriation at *ortho*, *meta* and *para* positions are $-7{\cdot}0 \pm 0{\cdot}3$, $-3{\cdot}0 \pm 0{\cdot}3$ and $-1{\cdot}0 \pm 0{\cdot}3$ ppb, respectively. This pattern is not the one expected if a simple mesomeric interaction is at play. It appears that two different mechanisms are involved.

Deuteriation at the S-ring gives rise to no measurable equilibrium isotope effects. This is not easily explained. The S-ring seems to be mesomerically coupled to the remainder of the system as substituents at the S-ring change the equilibrium position as judged from ^{13}C NMR data[20] and also the UV spectrum, althougn to a lesser extent than substituents at the O-ring.[22] The occurrence of counteracting effects in the penta-deuteriated derivative is ruled out as the *o*-deuteriated species showed no isotope effect either.

The C—H stretching frequencies decrease on going from acetic acid to the acetate ion. It is hence understandable that deuteriation will reduce the acidity. Weston,[23] in a discussion of the decrease in the acidity constant on perdeuteriation of benzoic acid, referred to this fact. In view of the finding that the CD_3 and the C_6D_5 groups behaves similarly toward a carbonyl group, it seems reasonable that deuteriated acetate and benzoate will behave similarly. It is therefore not necessary or advisable[24] to assume that deuterium is an electropositive substituent, as has been postulated before.[6] Working along those lines, Künzer and Berger[14,15] determined the Hammett–Taft parameter, σ_I, for deuterium. This approach is questionable and their results are at variance with the findings in this study.

Klein and Streitwieser[13] investigated the dissociation of deuteriated benzoic acid and concluded that the effect of deuterium seems to be distributed roughly evenly about the ring, the C—D bond behaving as a normal inductive substituent and decreasing the acid strength. Bernasconi *et al.*[25] concluded that only deuteriation in the *ortho* position affected the dissociation constant of the anilinium ion, again decreasing the acid strength. Kresge *et al.*[26] found that deuteriation in *ortho*, *meta* and *para* positions is equally effective in increasing the ionization of triphenylmethyl chloride. The three results do not fully agree. A kinetic study of the solvolysis of benzhydryl chloride gave an acceleration by deuteriation at the *ortho*, *meta* and *para* positions of 1·9%, 1·5% and 1·0% per deuterium, respectively.[27] Streitwieser and Klein[27] concluded that the isotope effect measures both

the inductive and the field effect polarizations in the σ-bond system.

Deuteriation at the O-ring shows in our case a decrease in the order *ortho* > *meta* > *para*. This order is not a simple dependence on mesomeric effects. Two types of vibrations clearly have to be taken into account, the C–H stretching and the C–H bending vibrations.[24] However, to improve the model, the strong interaction between the C–C stretching in the aromatic ring and the C–H bending vibrations must be included.[28] The different C–D bending vibrations will then affect the carbon skeleton vibrational energies. We are therefore left with two effects: one coupled to the carbon skeleton σ-system and most likely levelling off with increasing distance from the reaction centre, and another coupled to the π-system, independent of the ring position.

The net effect will be the sum of the two effects and, further, their relative strengths may be determined by the nature of the reaction centre, thereby causing the apparent experimental confusion in previously published papers.

Scrambling reactions

The scrambling reaction mechanism occurring during acetylation of the deuteriated benzenes cannot be fully explained on the basis of these results. However, some conclusions can be drawn. The exchange of deuterium due to moisture is not a major event, judging from the experiment using hexadeuteriobenzene. The fact that acetylation of 1,4-dideuteriobenzene leads to both tri- and tetra-deuteriated derivatives shows that intermolecular transfer takes place. If transfer occurs to the acetophenones, extra deuteriums should occur primarily in positions *meta* to the acetyl group and tetrasubstituted derivatives should not be formed. This is not in accord with the experimental findings, which show a large amount of trideuteriated benzophenone with a label in the *ortho*, *meta* and *para* positions. Transfer to *meta* positions should lead to either 3,4,5- or 1,2,4-trideuterioacetophenone. As acetophenone is less reactive than benzene itself, it is conceivable that transfer takes place directly to 1,4-dideuteriobenzene. This would lead to 1,2,4-trideuteriobenzene plus monodeuteriobenzene. Acetylation of the former leads to three different trideuteriated acetophenones, 2,3,6- 2,3,5- and 2,3,6-trideuterioacetophenone, all in agreement with the findings in Table 2. Further deuteriation of 1,2,4-trideuteriobenzene leads to three different tetradeuteriated benzenes, 1,2,5,6-, 1,2,3,4- and 1,2,3,5-tetradeuteriobenzene. Acetylation of these leads to the three possible tetradeuterioacetophenones (plus a number of trideuterio derivatives). Only two tetradeuteriated acetophenones have been found, but the amounts expected are so small that the third may have escaped detection.

The observation of substantial amounts of trideuteriated acetophenones with deuterium in *ortho*, *meta* and *para* positions together with the fact that deuterium transfer to the acetophenone cannot lead to tetradeuterioacetophenones, and also that benzene is more reactive than acetophenone in an electrophilic substitution reaction, point to an intermolecular deuteriation of 1,4-dideuteriobenzene, leading to 1,2,4-trideuteriobenzene and further to tetradeuteriobenzenes. The present study is not a proof that this is the only reaction pathway as it does not rule out 1,2-Jacobsen shifts or that transfer to acetophenone does not occur to a minor extent.

EXPERIMENTAL

Materials. All β-thioxoketones, whether deuterated or not, were prepared by base-promoted Claisen condensation reaction of the pertinent methyl ketones with appropriate thiono- or dithioesters.[11,12] The procedure was modified in order to minimize the amount of deuteriated material used. A special procedure was used for the synthesis of (formal) 1,1,1,3,3-pentadeuteriothioacetylacetone (see below).

Acetophenones deuterated in the aromatic ring were prepared from deuteriated benzenes by a Friedel–Crafts reaction procedure following the Perrier method[17] but using either CS_2, CCl_4 or CH_2Cl_2 as solvent, and using benzene, acetyl chloride and aluminium chloride in the ratio 1 : 1·1 : 1·2. Monodeuteriated benzene was prepared by a Grignard reaction following standard procedures and 1,4- and 1,3,5-trideuteriobenzene were obtained from Merck, Sharp and Dohme. Acetophenone deuteriated in the methyl group was provided by Stable Isotopes (Switzerland).

Thiono esters were synthesized from the corresponding nitriles via the derived imino ester hydrochlorides as described by Schmidt *et al.*[29] Ethyl dithiobenzoate was synthesized from bromobenzene via reaction with the derived Grignard reagent with carbon disulphide and, subsequently, ethyl iodide, as described by Meier *et al.*[30] The same procedure was followed for the synthesis of ethyl 2-deuteriodithiobenzoate, using 2-deuteriobromobenzene as starting material. The latter was prepared from 2-bromoaniline after treatment with D_2PO_2, D_2SO_4 and sodium nitrite.[31]

1,1,1,3,3-Pentadeuteriothioacetylacetone. A 12·8 g (0·2 mol) amount of hexadeuterioacetone (Aldrich) in 100 ml of dry diethyl ether was added dropwise over 30 min to 118 ml of a stirred 1·7 M solution of *tert*-butyllithium in pentane (Aldrich) kept below 0 °C under an atmosphere of nitrogen. Stirring was then continued for a further 30 min (temperature below 0 °C, nitrogen atmosphere). Then 10·4 g (0·1 mol) of

ethyl thionoacetate[29] in 50 ml of dry diethyl ether were stirred in dropwise over 30 min (temperature below 0 °C, nitrogen atmosphere). Stirring was continued for 16 h, during which the temperature of the reaction mixture was allowed to rise to room temperature. A 200-ml volume of D_2O was added with vigorous stirring, initially dropwise, over 5 min. The two layers were separated and the organic layer was extracted with a further 50 ml of D_2O. The combined aqueous layers were washed twice with 100 ml of diethyl ether, then 200 ml of diethyl ether were added, followed by 50 ml of *ca* 9% DCl in D_2O with manual stirring. The layers were separated and the yellow etheral layer was washed twice with 50 ml of D_2O and dried (Na_2SO_4). The ether was removed by rotary evaporation to leave 7·0 g of a dark-yellow oil, which was distilled through a short Vigreux column to yield 4·45 g (32%) of (formal) 1,1,1,3,3-pentadeuteriothioacetylacetone as a golden-yellow oil, b.p. 69–70 °C/15 mmHg.

NMR spectra. The ^{13}C and ^{1}H spectra were recorded on Bruker AC 250, HX 270 and AM 500 NMR spectrometers operating at 62·9, 67·9 and 125·7 MHz for ^{13}C, respectively. The temperature was 300 K except in the temperature experiments. Chemical shifts are quoted relative to internal TMS. The solvent was $CDCl_3$. The ^{13}C NMR spectra were recorded using broad-band ^{1}H decoupling. The digital resolution was 0·5–1 Hz per point. Concentrations were *ca* 70 mg ml^{-1}. The ^{1}H NMR spectra were recorded using a digital resolution of 0·15 Hz per point. Concentrations were *ca* 2 mg ml^{-1}.

ACKNOWLEDGEMENTS

The authors thanks Drs Helge Egsgard and Elfinn Larsen, Riso National Laboratory, for their kind help in obtaining the mass spectra. The assistance of Anne-Lise Gudmundson and Annette Syberg Henriksen in synthesizing some of the compounds is greatly appreciated. The authors also thank the Danish Natural Science Council for support and for the use of the Bruker HX 270 and AM 500 spectrometers.

REFERENCES

1. A. V. Willi, *Isotope Effekte bei Chemischen Reaktionen.* Georg Thieme, Stuttgart (1983).
2. L. Melander and W. H. Saunders, *Reaction Rates of Isotopic Molecules.* Wiley-Interscience, New York (1980).
3. H. Batiz-Hernandez and R. A. Bernheim, *Prog. Nucl. Magn. Reson. Spectrosc.* **3**, 63 (1967).
4. P. E. Hansen, *Annu. Rep. NMR. Spectrosc.* **15**, 105 (1983).
5. P. E. Hansen, *Prog. Nucl. Magn. Reson. Spectrosc.* **20**, 207 (1988).
6. E. A. Halevi, *Prog. Phys. Org. Chem.* **1**, 109 (1963).
7. M. Saunders, personal communication in Ref. 8.
8. H. U. Siehl, *Adv. Phys. Org. Chem.* **23**, 63 (1987).
9. P. E. Hansen, P. Schmitt and F. Duus, *Org. Magn. Reson.* **18**, 58 (1982).
10. F. Duus, *J. Am. Chem. Soc.* **108**, 630 (1986).
11. L. Carlsen and F. Duus, *Synthesis* 256 (1977).
12. F. Duus, *Synthesis*, 256 (1985).
13. H. S. Klein and A. Streitwieser, Jr, *Chem. Ind. (London)* 180 (1961).
14. H. Künzer and S. Berger, *Tetrahedron Lett.* **25**, 5019 (1984).
15. H. Künzer and S. Berger, *J. Am. Chem. Soc.* **107**, 2804 (1985).
16. H. J. Reich and D. J. Cram, *J. Am. Chem. Soc.* **91**, 3505 (1969).
17. D. T. Mowry, M. Renoll and W. F. Huber, *J. Am. Chem. Soc.* **68**, 1105 (1946).
18. C. H. Arrowsmith and A. J. Kresge, *J. Am. Chem. Soc.* **108**, 7918 (1982).
19. P. E. Hansen, F. M. Nicolaisen and K. Schaumburg, *J. Am. Chem. Soc.* **108**, 625 (1986).
20. P. E. Hansen and F. Duus, unpublished results.
21. D. C. McKeen, *Chem. Soc. Rev.* **7**, 399 (1978).
22. L. Carlsen and F. Duus, *J. Chem. Soc., Perkin Trans. 2* 1768 (1980).
23. R. E. Weston, *Tetrahedron* **6**, 31 (1959).
24. E. R. Thornton, *Annu. Rev. Phys. Chem.* **17**, 349 (1966).
25. C. Bernasconi, W. Koch and H. Zollinger, personal communication in Ref. 6.
26. A. J. Kresge, K. N. Rao and N. N. Lichtin, *Chem. Ind. (London)* 53 (1961).
27. A. Streitwieser and H. S. Klein, *J. Am. Chem. Soc.* **86**, 5170 (1964).
28. D. H. Whiffen, *Philos. Trans. R. Soc. London Ser. A* **248**, 131 (1955).
29. U. Schmidt, E. Heyman and K. Kabitzke, *Chem. Ber.* **96**, 1478 (1963).
30. J. Meier, P. Vermeer and L. Brandsma, *Recl. Trav. Chim. Pays-Bas* **92**, 601 (1973).
31. D. V. Banthorpe, E. D. Hughes, C. Ingold and R. Humberlin, *J. Chem. Soc.* 3299 (1962).