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Saeed Bahjat (Orcid ID: 0000-0002-0288-5389)

Hansen Poul Erik (Orcid ID: 0000-0003-4751-9910)

Strong Intramolecular Hydrogen Bonds and steric Effects involving C=S groups. An NMR and Computational Study.

Rita S. Elias[a], Bahjat A. Saeed[b*], Fadhil S. Kamounah[c], Fritz Duus[d] and Poul Erik Hansen[d]

[a] Department of Pharmaceutical Chemistry, College of Pharmacy, University of Basrah, Iraq.

[b] Department of Chemistry, College of Education for Pure Sciences, University of Basrah, Iraq.

[c] Department of Chemistry, University of Copenhagen, Universitetsparken 5, DK-2100 Copenhagen, Denmark

[d] Department of Science and Environment, Roskilde University, Universitetsvej 1, DK-4000 Roskilde, Denmark

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Abstract:

A number of 5-acyl rhodanines and thiorhodanines with bulky acyl groups (pivaloyl and adamantoyl), not previously available, have been synthesized. The compounds are shown to exist in the enol form. Structures have been calculated using both the MP2 approach and the B3LYP-GD3BJ functional and the 6-311++G(d,p) basis set. Hydrogen bond energies are estimated by subtracting energies of a structure with the OH group turned 180° from that of the intramolecularly hydrogen bonded one. Properties such as OH chemical shifts, two-bond isotope effects on ^{13}C chemical shifts, electron densities at the bond critical point from AIM analysis, as well as the hydrogen bond energies show that the sterically hindered compounds have stronger hydrogen bonds than methyl or isopropyl derivatives. The combination of oxygen and sulphur derivatives enables a detailed analysis of hydrogen bond energies.

1 INTRODUCTION

Hydrogen bond strength is related according to the definition of hydrogen bonds to the XH chemical shift, the XH stretching frequency and the XH bond length [1] and for a long time also to the heavy atom distance [2]. Nuclear Magnetic Resonance (NMR) is in terms of XH chemical shifts, X being O, N or S, deuterium isotope effects on chemical shifts[3] and primary isotope effects [4,5] very useful tools in the investigation of intramolecular hydrogen bonding. It has been assumed that a short heavy atom distance (X…X) in the intramolecular hydrogen bond e.g. O…O in Fig. 1 would lead to a strong hydrogen bond [6]. Short X…X distances normally leads to a large XH (X being O or S) chemical shift and a large two-bond isotope effects on ^{13}C chemical shifts, $^{2}\Delta C(OD)$ [7]. However, the assumption of a correlation between a short X…X distance and the strength of the hydrogen bond has recently been questioned especially if the compression is caused by steric strain [8], whereas the opposite, short distance is determining the strength, has also been claimed. [6]

A short X…X distance can in some cases be obtained by steric compression. Steric effects in *o*-hydroxyacyl aromatics have been found to be of two kinds leading either to a twist of the acyl group out of the ring plane or to steric compression. [9] In the former case this leads to a weaker hydrogen bond, in the latter case to a "stronger" hydrogen bond at least as expressed as a larger OH chemical shift and a larger two-bond isotope effect.

Systems like 2-acyl Meldrums acid [10], 5-acyl-3-methylrhodanines (RO-type) [11], 5-acyl-3-methyl-4-thiorhodanines [12] (RS-type) and 5-acyl-2-thiobarbituric acid[13] all exist at least partly in the enolic form (for RO- and RS- see Fig.1 or Scheme 1). However, so far it has not been possible to introduce bulky groups like a pivaloyl or adamantoyl group, Z being a *tert*-butyl or an adamantyl group. An exception is in 3-acyltetronic acids, but this is a complicated system as averaging is taking place.[14]

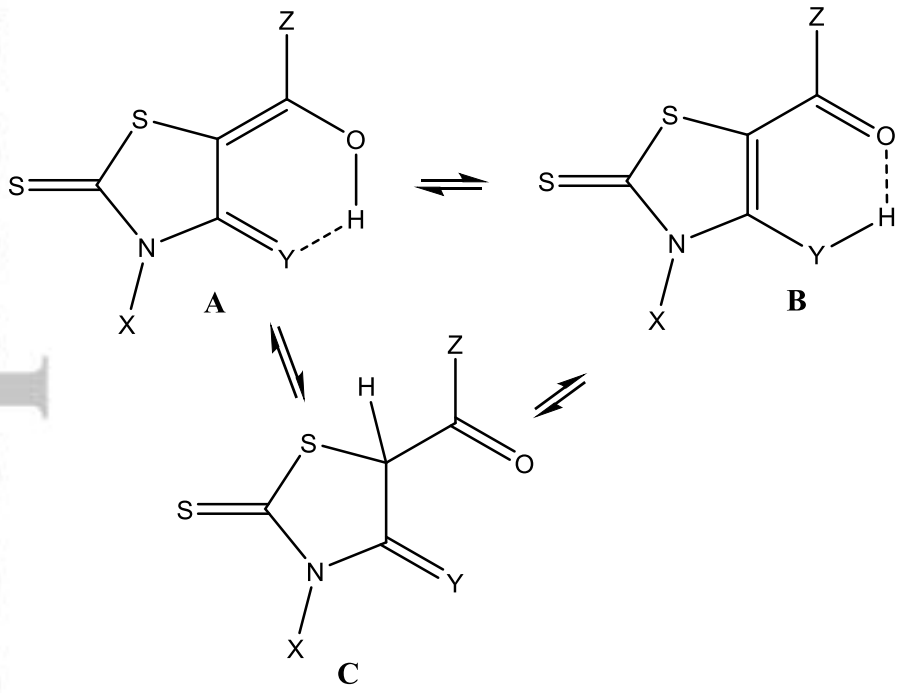
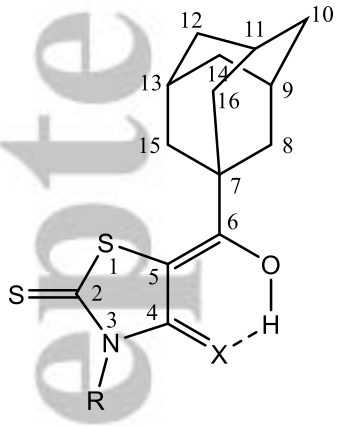


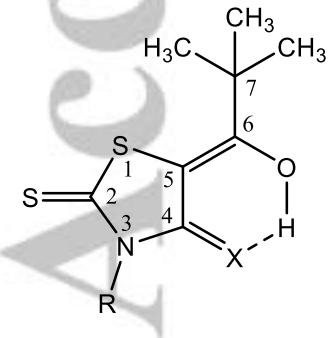
Fig. 1. Possible tautomeric structures of the investigated compounds.

When Y = O the compound is abbreviated RO- and when Y= S it is called RS-.

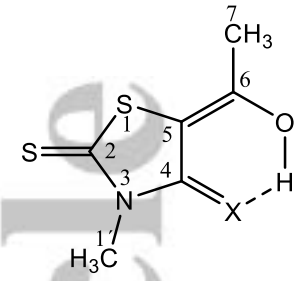
In the present study we have succeeded in making Z= *tert*-butyl as well as Z= adamantyl derivatives of both the 5-acyl-3-methylrhodanines (Y=O) and the 5-acyl-3-methyl-4-thiorhodanines (Y=S). As shown in Fig. 1 These two systems, because of the exocyclic double bond (see Fig. 1), will show steric compression. The effect on hydrogen bond strength is demonstrated by MP2 calculations according to Cuma, Scheiner and Kar [15] and Grabowski. [16,17] The idea is to calculate the energy for the hydrogen bonded case and subtracting the energy of the species with the OH bond turned 180°. This approach is called hb and out. This approach requires that no new interactions occur in the species with the OH bond turned and repulsion could also be a problem. [16,17] This approach will also be discussed. Atoms in Molecules (AIM) analysis has also been used to analyze hydrogen bond strength in intra-molecularly hydrogen bonded systems. [18] These parameters are then correlated with NMR parameters such as OH chemical shifts and two-bond deuterium isotope effects on ^{13}C chemical shifts



1 R=CH_3, X=O
2 R=Ph, X=O
3 R=CH_3, X=S
4 R=Ph, X=S



5 R=CH_3, X=O
6 R=Ph, X=O
7 R=Ph, X=S
8 R=CH_3, X=S



9 X=O
10 X=S

Scheme 1. Compounds **1**, **2**, **5**, **6** and **9** are of O-type (RO-compounds) and compounds **3, 4, 7** ,**8** and **10** are of S-type (RS-compounds).

2 Results

2.1 Nuclear Magnetic Resonance measurements

The NMR data are given in Table 1 and in Suppl. mat. Tables 1aS and 1bS. It is seen that a considerable increase is found in the XH chemical shift (as seen in Discussion, X=O) for both the RO- and RS-type of molecules on going from small substituents, Z of Fig. 1, to large substituents, as exemplified for the RS-type: methyl (15.08 ppm) (**10**), [12] benzyl (15.15 ppm) [13], isopropyl (15.29 ppm) (**12**) compared to the sterically compressing *tert*-butyl and adamantyl giving ~16 ppm (Table 1).

Table 1. Selected ^{1}H and ^{13}C NMR data (in ppm) of compounds **1**-**7** ($CDCl_3$**)**. [a]

Atom/compd.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
OH[b]	14.01	13.94	16.41	16.34	13.98	13.91	16.21
C4	172.7	172.8	186.2	186.8	172.6	172.6	186.5
C5	95.6	95.7	108.8	109.3	95.8	95.9	109.3
C6	179.9	180.2	184.1	184.8	180.4	180.7	185.3

a. A full set of ^{1}H and ^{13}C NMR chemical shifts are given in Suppl. mat. Tables 1aS and 1bS

b. This is given as OH. See Discussion

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

Values are given in Table 2. It is seen that the two-bond deuterium isotope effect on ^{13}C chemical shifts, $^{2}\Delta$C-6(OD), are increasing from RO- to RS-compounds. Comparing the data for **3**, **4** and **7** with those of non-sterically hindered compounds like Z=-isopropyl, Y=S, X=methyl (**12**) with a two-bond isotope effect of 0.76 ppm, an increase is also seen. For this compound a $^{4}\Delta$C-4(OD) = -0.43 ppm [19] is less negative than found for **3**, **4** and **7**.

Table 2. Isotope effect of ^{13}C chemical shifts of compounds **1**-**7** in ppm. Experimental and computed values ((MPW91PW1/6-311+G(2d,p)).

Carbon/ compound	**1**[a]	**2**	**3**[b]	**4**	**5**	**6**	**7**
C2	---	-0.07 (-0.05)	-0.13 [-0.14] [b] (-0.06)	-0.16 (-0.06)	-0.08 (-0.04)	-0.08 (-0.04)	-0.19 (-0.07)
C4	---	0.1 (0.17)	-0.57 [-0.54] [b] (-0.22)	-0.94 (-0.24)	0.12 (0.14)	0.1 (0.18)	-1.1 (-0.21)
C6	0.62 (0.52)	0.59 (0.52)	0.83 [0.8] [b] (0.45)	1.0 (0.45)	0.65 (0.55)	0.6 (0.53)	1.08 (0.46)
C5	---	-0.02 (-0.14)	---	-0.07 (-0.11)	-0.05 (-0.15)	-0.02 (-0.16)	-0.07 (-0.12)
C1’	---	-0.02 (-0.04)	---	-0.07 (-0.05)		-0.02 (-0.03)	-0.08 (-0.05)
C7	---	0.08 (0.05)	0.12 (0.05)	0.17 (0.05)	0.08 (0.06)	0.07 (0.04)	0.17 (0.05)

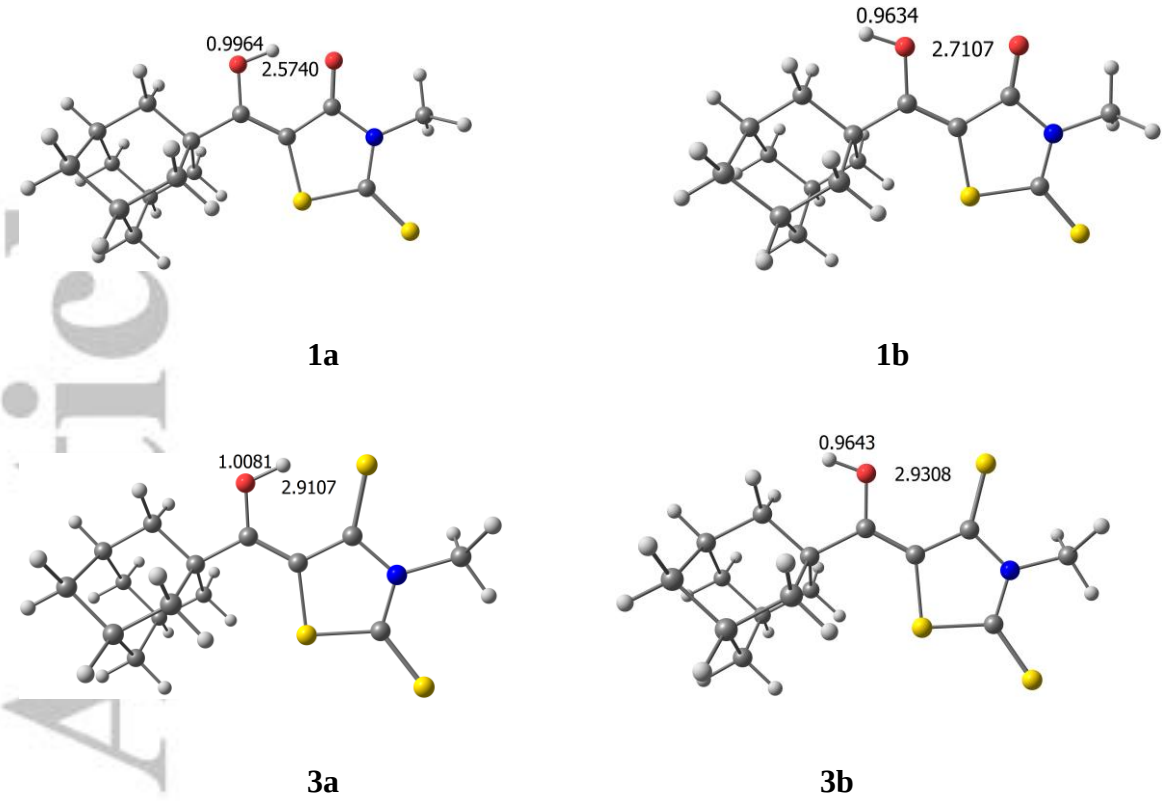
[a] Values in brackets are calculated isotope effects based on a bond shortening of 0.01Å (see **2.3.5**).

[b] 233K

2.3 Calculations

2.3.1 Structures. For compounds **1-7** two different conformations regarding the *t*-butyl or the adamantyl groups are considered. Either one with the CH_3 or CH_2 groups eclipsed vs. the C=O respectively C=S group or one in which a gauche conformation is assumed. Only in compound **3** has it been possible in the MP2 calculations to obtain both forms. For **3** the eclipsed form has the lowest energy. The energy difference between eclipsed and gauche form is ~4 KJ. However, calculating the difference in energy between the hydrogen bonded and the open form almost the same energy is found. For the methyl derivatives **9** and **10** the two methyl rotor positions have approximately the same energy. For the N-phenyl derivatives the phenyl group is twisted heavily out of the ring plane (~90°). For **3** the N-methyl rotor position is important. The one being eclipsed to C-2 has the lowest energy.

The OH bond lengths are clearly different for RO- and RS-types (Scheme 2) and for normal (**9** and **10**) vs. sterically compressed compounds (**1-7**) (see Schemes 1Sa and 1Sb). The O…O and O…S distances are likewise shorter in the sterically hindered derivatives. The O…O distance is larger in the non-hydrogen bonded cases than in the hydrogen bonded ones, whereas for the O…S distances no great difference is seen between the hydrogen bonded and open forms. A comparison of the hydrogen bonded and the non-hydrogen bonded structures calculated at the B3LYP-GD3BJ/6-311++G(d,p) are given in Scheme 2.



1a **1b**

3a **3b**

Scheme 2. Optmized structures of compounds **1** and **3** calculated at the B3LYP-GD3BJ/6-311++G(d,p) level of theory. **a** refers to the hydrogen bonded form. **b** refers to a non-hydrogen bonded (open) form. More data are given in Table 2S and Schemes 1Sa and 1Sb in the Suppl. Mat.

Comparing all bond lengths in the hydrogen bonded and the open forms give results akin to resonance assisted hydrogen bonding in the sense that in the hydrogen bonded form the OH bond length is longer, the C-O bond short, the C=C bond longer, the C-C bond shorter and the C=Y bond longer. Furthermore, this feature is more pronounced when R is *tert*-butyl and adamantyl than when it is methyl.

2.3.2 Atoms in Molecules analysis. The electron densities (ρ) and the Laplacian of the electron densities ($\nabla^2\rho$) at bond critical points (BCP) are given for relevant distances in Table 3. AIM figures showing both Electron densities and their Laplacian for the hydrogen bonded and the open forms are presented in Schemes 2Sa to 2Sd in the Suppl. Mat.

Table 3. Electron densities (ρ) and Laplacian ($\nabla^2\rho$) at bond critical points for **1-10**.

Molecule	Atoms	Bonded OH		Atoms	Free OH	
		Rho	Laplacian		Rho	Laplacian
1	H6 – O4	0.0520	0.1442	H6 – C8	0.0218	0.0838
	H15 – S1	0.0116	0.0352	H15 – S1	0.0138	0.0412
	H16 – S1	0.0116	0.0352	H16 – S1	0.0138	0.0412
2	H6– O4	0.0522	0.1441	H6 – C8	0.0216	0.0835
	H15 – S1	0.0116	0.0352	H15 – S1	0.0138	0.0413
	H16 – S1	0.0116	0.0352	H16– S32	0.0138	0.0413
3	H6 – S4	0.0506	0.0547	H6 – C8	0.0228	0.0866
	H1' – S2	0.0168	0.0545	H3 – S4	0.0169	0.0553
	H15– S1	0.0138	0.0412	H15 – S1	0.0125	0.0445
	H16 – S1	0.0138	0.0412	H16 – S1	0.0125	0.0445
4	H6 – S4	0.0515	0.0532	H6 – C8	0.0228	0.0865
	H15 – S1	0.0139	0.0413	H15 – S1	0.0151	0.0448
	H16 – S1	0.0139	0.0413	H16– S1	0.01515	0.0448
5	H6 – O4	0.0521	0.1442	H6 – C8	0.0215	0.0831
	H10 – S1	0.0108	0.0335	H9– S1	0.0128	0.0392
	H9 – S1	0.0108	0.0335	H10 – S17	0.0128	0.0392
6	H6 – O4	0.0553	0.1511	H6– C8	0.0209	0.0803
	H10 – S1	0.0101	0.0363	H9– S17	0.0123	0.0427
	H9– S1	0.0101	0.0363	H10 – S17	0.0123	0.0427
7	H6 – S4	0.0516	0.0528	H6 – C8	0.0244	0.0856
	H10– S1	0.0127	0.0391	H9– S1	0.0139	0.0424
	H9– S1	0.0127	0.0391	H10 – S1	0.0139	0.0424
8	H1'-S2 H6-S4	0.0166 0.0512	0.0540 0.0.539	H1'-S4	0.0167	0.0549
9	H6 – O4	0.0386	0.1298	---	---	---

10	H1'-S2 H6-S4	0.0167 0.0436	0.0543 0.0557	H1'-S4	0.0168	0.0550

2.3.3 Energies. Energies have been calculated using two different levels of theory MP2 and B3LYP-GD3BJ in conjunction with the 6-311++G(d,p) basis set in order to compare with published results.[16] It is obvious from Fig. 2 and Table 4 that the trends are similar but the values for B3LYP-GD3BJ are larger than for MP2. Calculations are performed both for the hydrogen bonded form and the open form as seen in Scheme 2 and the energy differences are plotted in Fig. 2 vs. the OH chemical shifts. In addition to compounds **1-7, 9** and **10** a structure **8**, Z= *tert*-butyl, X= CH_3 and Y= S is calculated as this compound has been synthesized, but not obtained in a pure form. Furthermore, two isopropyl derivatives **11** and **12** are calculated (Z= isopropyl, X= CH_3 and Y= O or S), respectively.

Table 4. OH chemical shifts, MP2 [a] and B3LYP-GD3BJ [a], ΔE [b] values and O….X distances.[c]

Compounds	OH Chemical shifts (ppm)	MP2 ΔE KJ mol^{-1}	B3LYP-GD3J ΔE KJ mol^{-1}	$R_{O....X}$ [d] (Å)
1	14.01	53.9	57.9	2.5498
2	13.93	54.3	58.3	2.5762
3	16.41	59.3	67.2(5)	2.9107
4	16.34	56.05	66.1	2.90897
5	13.98	56.2(5)	59.0(5)	2.5667
6	13.91	---	59.8	2.5732

7	16.21	---	67.8	2.9089
8	16.36	59.08	63.87	2.8879
9	11.74	50.4	53.7(5)	2.6270
10	15.08	56.0	61.2	2.9388
11	12.21 [e]	51.80	55.27	2.6300
12	15.29 [f]	56.60	62.87	2.9367

a. Basis set is 6-311++G(d,p)

b. ΔE is defined as the energy difference between the hydrogen bonded and the open derivative (see Experimental).

c. O…X equal to O…. O for RO-derivatives and O…. S for RS-derivatives. For distances calculated with B3LYP-GD3BJ see Table 1S.

d. O…X distances calculated with MP2/6-311++G(d,p)

e. From Ref. 13

f. From Ref. 12

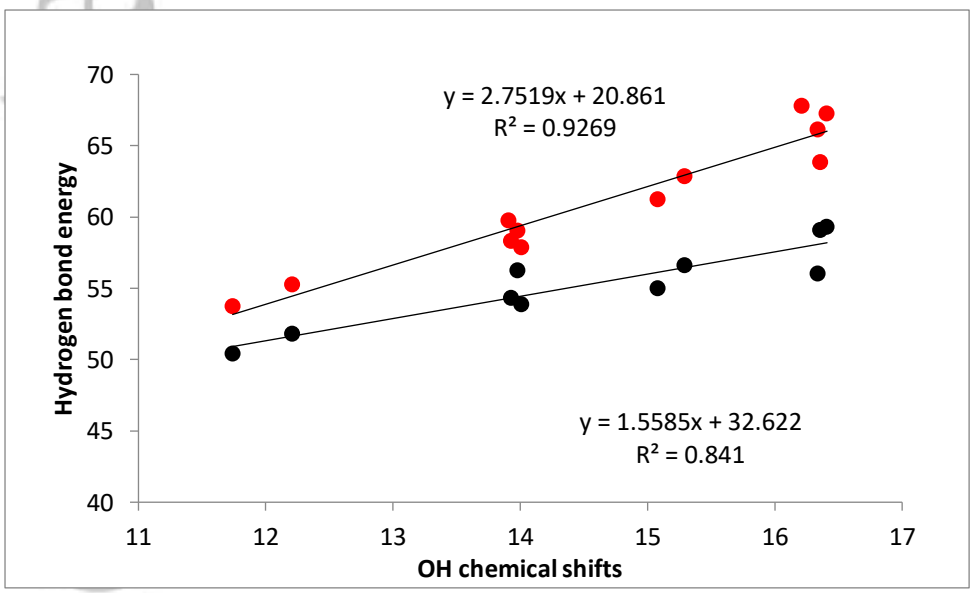


Fig. 2. Energy differences in KJ.mol^{-1} (see text) vs. OH chemical shifts (in ppm). Lower line is from MP2 and upper line is from B3LYP-GD3BJ calculations.

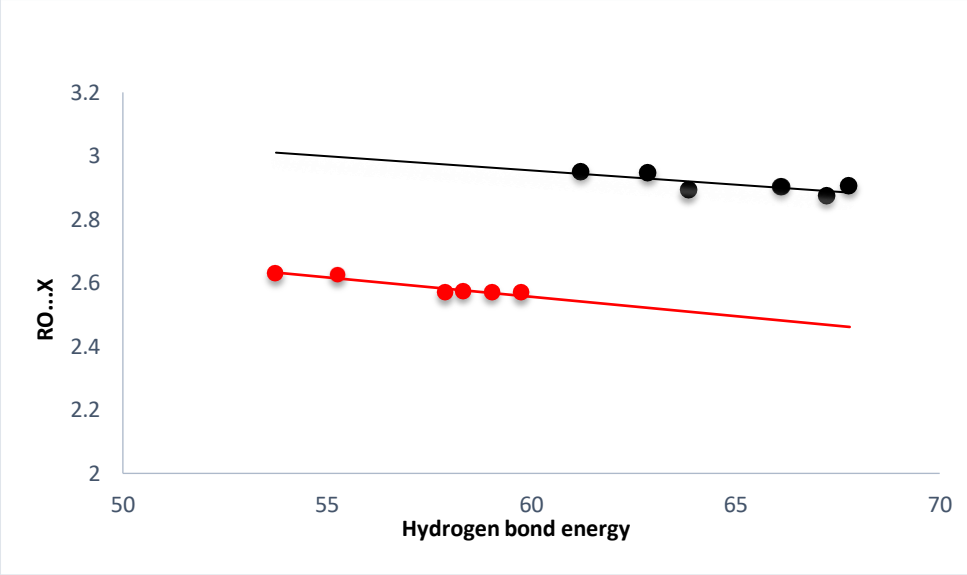


Fig. 3. Heavy atom distance (O…O for RO-derivatives (bottom line) and O…S for RS-derivatives (top line)) in Å vs. hydrogen bond energy ((B3LYP-GD3BJ) in KJ.mol^{-1}.

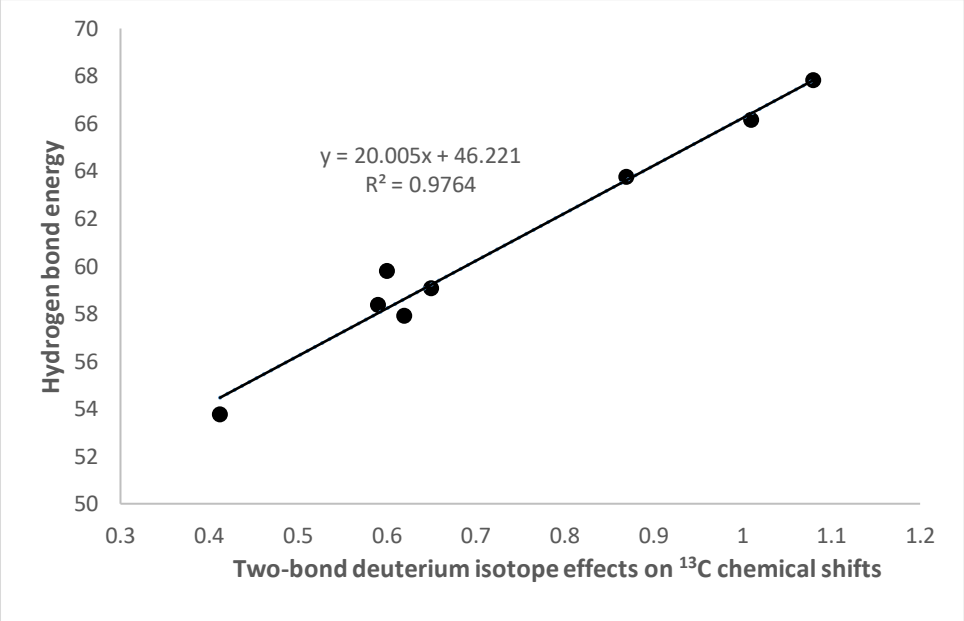


Fig 4. Hydrogen bond energy in KJ.mol^{-1} (B3LYP-GD3BJ) vs. two-bond deuterium isotope effects on ^{13}C chemical shifts (in ppm).

2.3.4 NMR chemical shifts. ^{13}C NMR nuclear shieldings (σ) have been calculated and correlated to experimental chemical shifts (δ_{exp}) as illustrated in Figs. 1S-7S and Tables 3S-9S in the Suppl. mat. A unified equation is found as: $\delta_{exp} = -0.9553 * \sigma + 177.63$; $R^2 = 0.9982$.

2.3.5 Calculation of deuterium isotope effects. Deuterium isotope effects on ^{13}C chemical shifts are calculated as the nuclear shielding of the normal compound minus the nuclear shielding of a compound with the OH bond shortened 0.01 Å. [5]

3 DISCUSSION

An important first point is to establish the structure of the investigated compounds. The fact that no CH proton (typically around 5.5 ppm) is observed in the ^1H spectra of any of compounds leave out structure C of Fig. 1. For the RO-derivatives an equilibrium between B and C was ruled out. [11] The very large XH chemical shifts also leave out the possibility of tautomerism between A and B in RS-derivatives, as SH chemical shifts usually are very small. [7] In other words, the A-form is the only form and the XH proton is of OH type. The A-form is further supported by the very good correlation between observed ^{13}C chemical shifts of the observed chemical shifts and the calculated nuclear shieldings (see Table 10S).

Table 2 shows some remarkable deuterium isotope effects on ^{13}C chemical shifts. First of all, the large two-bond isotope effects seen on C-6 in both the RO-and RS-derivatives. As discussed above, the compounds are not tautomeric. This is strongly supported by the isotope effects found at C-7. Carbon 7 is aliphatic and will have very similar chemical shifts in A and B type tautomers. The magnitude of these chemical shifts cannot be explained by equilibrium isotope effects (dominated by the chemical shift difference between the chemical shifts of the two tautomers, [5] but must be due to a three-bond isotope effect due to deuteriation at the OH proton of A-type (Scheme1). The very large negative four bond

isotope effects for **3, 4** and **7** are akin to those found in 2-hydroxythioacyl aromatics [20] and in hydroxyflavothiones [21] and is ascribed to the longer O…S distance in the RS-derivative, which changes the balance between transmission via the hydrogen bond (positive contribution) and via the normal bonds (negative contribution).

Atoms in Molecules (AIM) analysis (Table 3) is clearly important in two ways for this investigation. The electron density at the bond critical point and the Laplacian has been related to hydrogen bond energy [18] and analysis of bond critical points can help to pin point non-covalent interactions related to the calculation of hydrogen bond energies of the Hb and out type (see later). Of particular interest is the finding that $\nabla^2\rho$ is for H6-O4 increased in **1**, **2, 5** and **6** compared to **9** and also for H6-S4 in **3, 4** and **7** compared to **10**.

The energies of Table 4 are calculated in two ways, MP2 and B3LYP-GD3BJ. The former to related to published results [16,17,22] and the latter as it is much faster. Fortunately, only a more or less constant difference is found between the two types of calculations. It can be seen that for RO-derivatives, a rough correlation is found between RO…. O distances and energy and the same is found for RS-derivatives. However, a correlation between RO…X, X=O or S, cannot be found at all.

Perrin [8] has recently questioned the correlation between a short heavy atom distance, in this case either O…O or O…S and the strength of the hydrogen bond, whereas Sanz et al. [6] have claimed that the only factor governing the hydrogen bond strength in oxygen containing compounds is the O…O distance. The present compounds are very well suited to investigate the correlation between X…X distances and hydrogen bond strength and possibly also to suggest other useful parameters. The introduction of large Z substituents (Figure 1) such as *tert*-butyl or adamantyl will in the enolic form reduce the O…O or the O…S distances as seen in Scheme 2 and Table 4. The energy due to hydrogen bonding is estimated from calculations

either MP2 type or DFT B3LYP-GD3BJ using the 6-311++G(d,p) basis set in the normal hydrogen bonded case and subtracting the energy of the form in which the OH group has been turned 180º (here called hb and out, respectively). This method was demonstrated by Cuma, Scheiner and Kar[15] to be used for salicylaldehyde and since elaborated on by Grabowski.[16] Values are given in Table 4. A relevant question is of course the accuracy of such a method. One drawback could be structural changes in the open form. A key compound is **3**. The O…. S distance is clearly diminished compared to compound **10** (Z= CH_3). However, the O…. S distance of **3** in the hydrogen bonded form is only slightly shorter than that of the open form (Scheme 2). The much higher energy of the open form is not related to structural differences. Furthermore, from the AIM analysis (Table 3) it can be seen that the OH group in the open form forms a bond path to C-8 and that the interaction between H-15 and H-16 and S-1 is not markedly different in the hydrogen bonded and the open form. Furthermore, electrostatic repulsion has been mentioned as a problem in the open form.[22] This is strongly diminished in the sulphur derivatives.

From Fig. 4 a relationship it is also seen between two-bond deuterium isotope effects on ^{13}C chemical shifts and energy. The latter may have the advantage that isotope effects like OH chemical shifts may depend on ring current effects (see below) and energies for compounds for which the hb-out method cannot be used, can be estimated. The use of isotope effects on ^{13}C chemical shifts was originally suggested by Reuben[23] and later tested for amides.[24]

In the present compounds the hydrogen bond properties have been modified in two ways either by steric compression (going from simple alkyl substituents to *tert*-butyl or adamantyl groups) or by changing the acceptor atom from oxygen to sulphur. The results are for the *tert*-butyl and adamantyl derivatives of RO- and for both types of RS-derivatives (for a definition see Fig. 1) a lengthening of the OH bond a shift of the OH chemical shift to higher frequency and increased hydrogen bond energies as seen in Fig. 2. In case of going from

simple alkyl substituent to the sterically larger *tert*-butyl or adamantyl substituent a decrease of the O…O or O…S distances are found. From Fig. 3 it is also seen that in a rough way the energy and the O…X distance are related within the O…O or O…S derivatives.

The use of OH chemical shifts to define the hydrogen bond strength requires that the OH chemical shifts are not influenced by other factors. Could the increase be due to a more pronounced anisotropy effect in the sterically hindered compounds as the atoms come closer and anisotropy effects could become more pronounced? For the RS-derivatives only partly as judged from calculations of anisotropy effects, ~0.7 ppm [25,26]. The increase in the OH chemical shifts for RS- vs. RO-derivatives or for methyl vs. *tert*-butyl and adamantyl derivatives is therefore related to a longer OH bond length (as also predicted from MP2 and DFT calculations). The introduction of a large aliphatic group has no electron donating or electron withdrawing effects so the effect is on shortening the O…O or O…S distances (Scheme S1). As found in Scheme 1Sb the system is of RAHB type so the longer OH bond length is related to the shorter O…O or O…S distance in the sterically hindered cases. The finding of a larger two-bond deuterium isotope effect at C-6 is also an indication of a stronger hydrogen bond.[3,7,9]

The calculation of energies using the hb and out approach has been criticized because of the oxygen oxygen repulsion is not considered.[27] In the present context compound **3** plays a central role. The O…S distance of **3** in the open form is only slightly longer than that of the hydrogen bonded form (Scheme 2), so repulsion cannot play a role. The much lower energy of the hydrogen bonded form (Table 4) is therefore related to intramolecular hydrogen bonding.

The electron density at the bond critical point can also be used to gauge hydrogen bond strength.[28] In the present case it is seen that ρ is smaller for the methyl derivatives as

compared to the t-butyl or adamantyl derivatives (Table 3) again supporting a stronger hydrogen bond in the two latter types.

To summarize: A number of indicators, OH chemical shifts, two-bond isotope effects on ^{13}C chemical shifts, OH stretching frequencies, electron density at the bond critical point as well as energy differences between hydrogen bonded and open systems all point to a stronger hydrogen bond in sterically strained compounds in this system of RAHB type.

4 Experimental

4.1 Materials. All reagents and solvents were purchased from commercial suppliers and used without additional purification unless otherwise indicated.

4.2 Synthesis

Compounds **1, 2, 5** and **6** (5-adamantoyl and 5- *tert*-butyl-3-methylrhodanine, 5-adamantoyl and 5-*tert*-butyl-3-phenylrhodanine) are synthesized according to Duus.[29] To a stirred solution of methyl lithium 1.6 M solution in ether (12.5 mL, 20 mmol) cooled to below 0ºC (ice/salt bath) under nitrogen atmosphere was added cautiously a solution of the appropriate rhodanine derivatives (10 mmol) in dry THF (20 mL) dropwise during 30 min. The resulting pale-yellow solution is stirred for a further 30 min. Subsequently, a solution of the appropriate carboxylic acid chloride (20 mmol) in dry THF (10 mL) is added dropwise during 30 min under continuous stirring. The mixture is left stirring for 12-16 h (overnight). Water (40 mL) is added during 30 min with stirring. After the admixture of a further portion of water (40 mL), stirring is continued for 30 min, acidified with 4 M aqueous hydrochloric acid to pH= 1-2, the aqueous layer is extracted with chloroform (2 x 80 ml). The combined organic layers are washed with water until neutral, and dried with anhydrous sodium

sulphate. The solvent is removed by evaporation under reduced pressure and the crude products are recrystallized from ethanol.

Compounds **3**, **4** and **7 (**5-adamantoyl-3-methyl-4-thiorhodanine, 5-adamantoyl and 5-*tert*-butyl-3-phenyl-4-thiorhodanine) are synthesized from compounds **1, 2,** and **6** by reaction with P_2S_5 according to a previously described procedure.[30] The reactions are carried out strictly under nitrogen in a three necked round bottomed flask fitted with a reflux condenser, dropping funnel and mechanical stirrer. The flask is charged with a solution of phosphorous pentasulphide (5 mmol) dissolved in anhydrous 1,4-dioxane (5 mL), the reaction is heated to 120°C on an oil bath. Then a solution of 5-acyl derivatives of rhodanine (1.6 mmol) in anhydrous 1,4-dioxane (10 mL) is added dropwise during which time the reaction mixture turned red. The reaction mixture is maintained at reflux for additional 24 hrs. Properties for compounds **1-7** are given in Table 11S.

4.3 Instrumentation. The NMR experiments were recorded on a Bruker 400 Ultrashield Plus at 400 MHz for ^{1}H and 100 MHz for ^{13}C. The solvent was $CDCl_3$ also for low temperature experiments. TMS was used as reference. HRMS LC/MS were measured using a Dionex Acclaim RSLC 120 C18 2.2 µm 120 Å 2.1 x 50 mm column maintained at 40 °C carried out on a Bruker MicrOTOF-QII-system with ESI-source with nebulizer 1.2 bar, dry gas 8.0 l/min, dry temperature 200 °C, capillary 4500 V end plate offset -500 V. Infrared spectra were recorded as KBr disks on a Perkin-Elmer Spectrum 2000 FT-IR spectrophotometer in the 4000-370 cm^{-1} range with a resolution of 1 cm^{-1} (average of 10 scans). UV spectra were recorded in ethanol in a 1cm quartz cuvettes utilizing a Smimadzu UV-2600 spectrophotometer.

4.4 Deuteration

For the study of the isotope effect on the ^{13}C chemical shifts the studied compounds were deuterated by dissolving 20 mg of the compound in a mixture of CH_3OD-CH_3OH (80:20). The solvent removed by rotary evaporation and traces of solvent were removed under high vacuum pressure using an oil pump. The procedure was strictly done under dry nitrogen atmosphere. The spectra of the deuterated samples were recorded using $CDCl_3$ as solvent.

4.5 Theoretical calculations

Structures. The calculations of geometry optimization, vibrational frequency and shielding constants were performed using the Gaussian 09 set of programs.[31] For Atoms in Molecules (AIM) calculations the AIMAll (Version 19.02.13) [32] package was employed.

Because the studied compounds contain intra-molecular hydrogen bonding it is necessary to take dispersion into account when calculating their electronic structure. Accordingly, both the MP2 method [33] and the B3LYP-GD3BJ [34] dispersion corrected functional were used because they both take into account long range interactions. The two were used in conjunction with the 6-311++G(d,p) basis set.[35,36]

4.6 Nuclear shielding. The shielding constants were calculated mainly at the MP2 and MPW1PW91 levels of theory, using the 6-311+G(2d,p) basis set.[35,36] It was stated that the NMR data calculated with the MPW1PW91/6-311+G(2d,p) approach excellently agreed with the experimental data.[37] In all nuclear shielding calculations, the gauge including atomic orbitals (GIAO) [38] formalism was used. The IEFPCM[39] solvation model was adopted for modeling the solvent ($CHCl_3$) environment throughout the calculations of nuclear shielding.

5 Conclusion

In this study 5-acyl rhodanines and thiorhodanines with bulky substituents like *tert*-butyl and adamantyl groups at the exocyclic double bond were successfully synthesized. These compounds are very well suited to investigate the correlation between heavy atom X…X distances and hydrogen bond strength in conjunction with NMR. The compounds are shown to exist in the intramolecular hydrogen bonded enolic form. According to their OH chemical shifts and isotope effect on ^{13}C chemical shifts as well as Atoms in Molecule calculations the sterically hindered molecules with bulky substituents have stronger hydrogen bonds than those without steric compression.

Conflict of interest

The authors declare no conflict of interest.

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REFERENCES

[1] E. Arunan, G.R. Desiraju, R.A. Klein, J. Sadlej, S. Scheiner, I. Alkorta, D. C. Clary, R. H. Crabetree, J. J. Dannenberg, P. Hobza, H. G. Kjaergaard, A. C. Legon, B. Mennucci, D. J. Nesbitt, *Pure Appl. Chem*. **2011**, *83*,1619.

[2] G. L. Hofacker, Y. Marechal, M. A. Ratner, In the Hydrogen Bond, Schuster P, Zundel G, Sandofy C, Eds. North-Holland: Amsterdam, 1976, p.1.

[3] P. E. Hansen, *Molecules*, **2015**, *20*:2405.

[4] L. J. Altman, P. Laungani, G. Gunnarsson, H. Wennerstrom, S. Forsen, *J. Am. Chem. Soc*. **1978**, *100*, 8264.

[5] S. Bolvig, P. E. Hansen, *Current Org. Chem*. **2000**, *4*, 19.

[6] P. Sanz, O. Mo, M. Yanez, J. Elguero, *J. Phys. Chem. A*. **2007**, *111*,3585.

[7] J. Abildgaard, S. Bolvig, P. E. Hansen, *J. Am. Chem. Soc*. **1998**, *120*, 9063.

[8] C. L. Perrin, *Acc. Chem. Res.* **2010**, *43*,1550.

[9] P. E. Hansen, S. Bolvig, K. Wozniak, *J. Mol. Struct*. **2005**, *749*, 155.

[10] S. Bolvig, F. Duus, P. E. Hansen, *Magn. Reson. Chem*. **1998**, *36*, 315.

[11] L. B. Smith, P. E. Hansen, *Z. Phys. Chem*. **2008**, *222*, 1213.

[12] D. T. T. Ngo, N. T. Nguyen, F. Duus, P. P. K. Nguyen, *Science Techn. Devel*. **2009**, *12*, 14.

[13] P. E. Hansen, F. Duus, R. Neumann, A. Wesolowska, J. Sosnicki, T. S. Jagodzinski, *Polish J. Chem*. **2000**, *74*, 409.

[14] J. P. Hofmann, F. Duus. Bond AD, P. E. Hansen, *J. Mol. Struct*. **2006**, *790*, 80.

[15] M. Cuma, S. Scheiner, T. Kar, *J. Am. Chem. Soc.* **1998**, *120*, 10497.

[16] S. J. Grabowski, *J. Mol. Struct.* **2001**, *562*, 137.

[17] S. J. Grabowski, *J. Phys. Org. Chem*. **2004**, *17*, 18.

[18] F. Fuster and S. J. Grabowski, *J. Phys Chem. A.* **2011**, *115*, 10078.

[19] F. Duus, P. E. Hansen, Private communication.

[20] T. T. Nguyen, T. N. Le, F. Duus, B. K. Hansen, P. E. Hansen, *Magn. Reson. Chem*. **2007**, *45*, 245.

[21] T. K. Nguyen, P. K. Nguyen, F. S. Kamounah, W. Zhang, P. E. Hansen, *Magn. Reson Chem.* **2009**, *47*, 1043.

[22] S. J. Grabowski, *Annu. Rep. Prog. Chem., Sec. C.* **2006**, *102*, 131.

[23] J. Reuben, *J. Am. Chem. Soc*. **1986**, *108*, 1735.

[24] P. E. Hansen, E. Tüchsen, *Acta Chem. Scand*. **1989**, *43*, 710.

[25] P. E. Hansen, A. Kock, E. Kleinpeter, *Tetrahedron Lett*. **2018**, *59*, 2288.

[26] P. E. Hansen, A. Kock, E. Kleinpeter, To be published.

[27] P. E. Hansen, F. S. Kamounah, B. V. K. Hansen, J. Spanget-Larsen, *Magn. Reson. Chem*. **2007**, *45*, 106.

[28] R. F. W. Bader, Atoms in Molecules. A Quantum Theory; Oxford University press, New York, 1990.

[29] F. Duus, *Synthesis*. **1985**, 672.

[30] A. P. Grischuk, *Khim. Geterotsiklicheskikh Soedin*. **1966**, *2*, 372.

[31] Gaussian 09, Revision D.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheesman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr, J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Jyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian, Inc, Wallingford CT, 2013.

[32] AIMAll (Version 19.02.13), Kieth TA, TK Gristmill Software, Overland Park KS, USA, 2016 (aim.tkgristmill.com).

[33] C. Moller, M. S. Plesset, *Phys. Rev.* **1934**, *46*, 618.

[34] A. D. Becke, *J. Chem. Phys.***1993**, *98*, 5648.

[35] M. W. Lodewyk, M. R. Siebert, D. J. Tantillo, *Chem. Rev*. **2012**, *112*,1839.

[36] P. H. Willoughby, M. J. Jansma, T. R. Hoye, *Nature Protocols*. **2014**, *9*, 643.

[37] D. Vikic-Topic, L. Pejov, *Croatica Chem. Acta*. **2001**, *74*, 277.

[38] K. Wolinski, J. F. Hinton, P. Pulay, *J. Am. Chem. Soc.* **1990**, *112*, 8251.

[39] J. Tomasi, B. Mennucci, R. Cammi, *Chem. Rev*. **2005**, *105*, 2999.