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Published in:
Journal of Molecular Structure: THEOCHEM

DOI:
10.1016/j.molstruc.2016.04.075

Publication date:
2016

Document Version
Peer reviewed version

Citation for published version (APA):
Hansen, P. E., & Spanget-Larsen, J. (2016). Structural studies on Mannich bases of 2-Hydroxy-3,4,5,6-tetrachlorobenzene. An UV, IR, NMR and DFT study. A mini-review. *Journal of Molecular Structure: THEOCHEM*, *1119*, 235-239. https://doi.org/10.1016/j.molstruc.2016.04.075

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Structural studies on Mannich bases of 2-Hydroxy-3,4,5,6-tetrachlorobenzene. An UV, IR, NMR and DFT study. A mini-review.

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Abstract

Mannich bases of 2-Hydroxy-3,4,5,6-tetrachlorobenzene are chosen as an exemplary case for tautomeric Mannich bases. Molecular structures are calculated. OH stretching frequencies are rationalized based on DFT calculations. Intrinsic deuterium isotope effects on ^{13}C chemical shifts in the M-form are estimated based on OH bond lengths. The observed deuterium isotope effects on ^{13}C chemical shifts are demonstrated to be largely of equilibrium type except at ambient temperatures.

Keywords: Mannich bases, DFT calculations, tautomerism, pK_a differences

Based on a talk at the XXI International meeting Horizons in H-bond Research in honor of Professor Lucjan Sobczyk

1. Introduction

Mannich bases (MB) play an important role in hydrogen bond research as a model for non-resonance intramolecular hydrogen bonds that show tautomerism. The controlling factors for proton transfer in tautomeric systems are particularly interesting. Tautomerism can be studied by UV, IR and isotope effects on chemical shifts in solution often supported by density functional theory (DFT) calculations. A key system is provided by the Mannich bases of 3,4,5,6-tetrachlorophenol (those formed with dimethylamine or diethylamine are in the following abbreviated Cl_4MBdm (**1**) or Cl_4MBde (**2**), respectively). Excellent reviews by Koll and Wolschann [1,2,3] and Sobczyk [4,5] exist in which this system is considered.

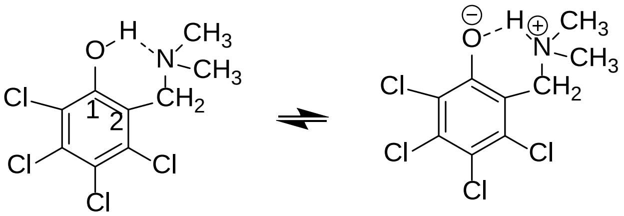
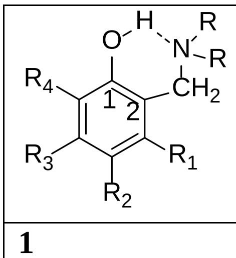


Figure 1. Structure of Cl_4MBdm (**1**) including tautomerism

Quantum chemical calculations are especially useful for tautomeric systems with fast interconversion as both tautomers usually cannot be isolated. DFT calculations may therefore provide information about structures, NMR chemical shifts and IR vibrations of both tautomers.

Table 1. Calculated compounds.

	R	R_1	R_2	R_3	R_4
1	CH_3	Cl	Cl	Cl	Cl
2	C_2H_5	Cl	Cl	Cl	Cl
3	Piperidino	Cl	Cl	Cl	Cl
4	Ethyl	Cl	Cl	H	Cl
5	Piperidino	Cl	Cl	H	Cl
6	CH_3	H	CH_3	H	CH_3
7	Piperidino	H	Cl	H	H
8	Morpholino	H	OCH_3	H	H
9	Pyrrolidino	H	Br	H	H

10	CH_3	H	NO_2	H	H
11	CH_3	H	Cl	H	Cl
12	CH_3	H	Cl	H	H

2. Results and discussion

2.1 Structure

Cl_4MBdm (**1**) can exist in two tautomeric forms as seen in Figure 1. This is also true for Cl_4MBde (**2**). The calculated structure of the molecular form (M-form) of (**1**) is seen in Figure 2; a distinct feature is the twist of the OH group out of the aromatic ring plane, as seen in the view to the left.

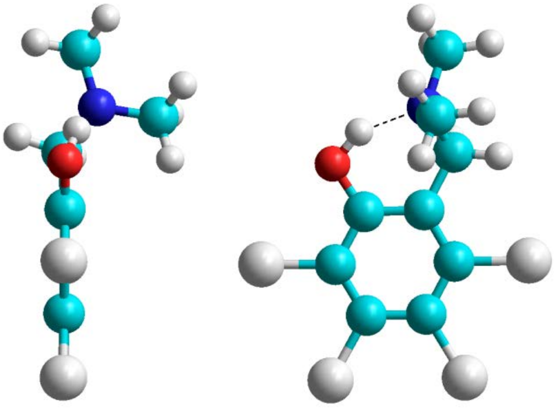


Figure 2. Calculated structure of the molecular form of Cl_4MBdm (**1**) seen from two different angles.

In case of the proton transfer form (PT-form) X-ray structures shows the presence of a dimer in the solid state. [4] For the 3,4,6-trichloro compound (**4**) a dimer has been demonstrated at low temperature in a freon solution [6] and one may assume this will also be the case for the tetrachloro compound in solution.

2.2 *UV spectroscopy*

The UV spectrum of Cl_4MBde (**2**) at different temperatures is given in Figure 3. [7]

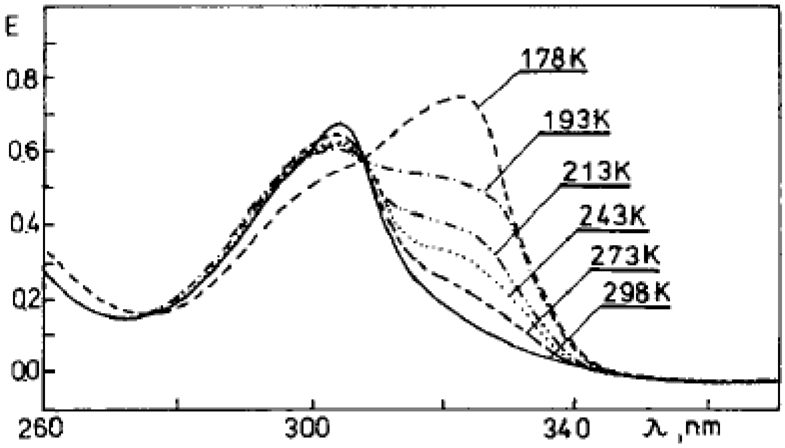


Figure 3. UV spectrum of Cl_4MBde (**2**) at different temperatures in CH_2Cl_2 taken from Ref. 7. (Reproduced with permission from Elsevier)

It is clearly seen that a new species is appearing at low temperature. This is assigned to the PT-form. [5] The red shift is consistent with the formation of a moiety containing a phenolate group as seen by titration of a Mannich base. [8]

2.3 *Infra Red spectroscopy*

A very large collection of IR spectra of MB was investigated with emphasis on the OH stretching vibrations (νOH). The νOH bands turn out to be both broad and very intense. [9] Compounds covering both electron withdrawing and electron donating substituents were included. The OH stretching frequencies were compared to those of the corresponding complex between the phenol and the amine. A clear cut change appeared for ΔpK_a around 3. ΔpK_a is defined as the pK_a difference between that of the phenol and that of the ammonium ion (see later). IR spectra of Cl_4MBdm as well as of the deuterated species have also been investigated in matrix isolation spectra in an argon matrix. A ratio of 1.33 is found between νOH and νOD. [10] In addition, IR spectra have been recorded in *n*-butylchloride. [5] These spectra showed a broad hump from 2500 cm^{-1} to 1600 cm^{-1}. This was suggested as being due to Zundel bands. However, a similar hump was not observed for the 4-nitroderivative. [2] A very distinct difference is seen between IR spectra of MB in the liquid and the solid state for cases with ΔpK_a larger than 4. This difference can be attributed to the presence of the PT form in the solid. [4]

Theoretical calculations of OH stretching frequencies have been performed for both the 2,4-dichloroMB and Cl_4MBdm. Although using a scaling factor of 0.95, a good fit for the B3LYP/6-31++G(d,p) model was not obtained. [10] Following the suggestion of Refs. [11,12] OH stretching frequencies have been calculated using the B3LYP model [13] with the 6-31G(d) basis. As this basis set is rather small, the calculations have been checked with a larger basis set, cc-pVTZ. The B3LYP results for the compounds **1-11** (Table 1) with the 6-31G(d) and cc-pVTZ basis sets are found to be linearly related:

$$\nu\text{OH(cc-pVTZ)} = -83.933 + 1.0416 \cdot \nu\text{OH(6-31G(d))} \qquad (\text{SD} = 9.25\ \text{cm}^{-1}, \text{R} = 0.99787)$$

The experimental OH stretching wavenumbers are plotted vs. the B3LYP/6-31G(d) results in Figure 4 and a very good correlation is found. It must be pointed out that the calculations are performed in vacuum. However, the IR spectra are recorded in a very low dielectric medium, either in CCl_4 (**4-10** [9]) or in an argon matrix (**11** and **1** [10]). The equation of Figure 4 allows a prediction of experimental OH stretching frequencies.

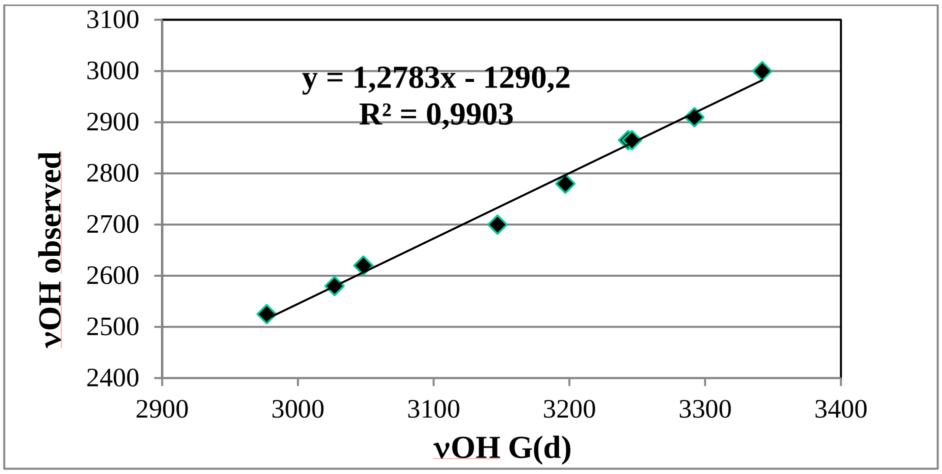


Figure 4. Plot of the observed OH stretching wavenumbers versus the calculated ones (B3LYP/6-31G(d)) for compounds **1**, **4-11**.

Looking at the calculated structure (Figure 2) it is seen that the OH group is twisted ~15^o out of the aromatic ring plane. This twist is the same using basis sets like 6-31G(d) or G-311++(d,p). A twist of this kind has led to a low OH chemical shift in e.g. 1-acetyl-2-hydroxynaphthalene and similar compounds. [14] This is not the case in the Mannich bases. Furthermore, the hydrogen bond potential is asymmetric judging from the ratio between νOH and νOD (see above). Comparing the Cl_4MB with a piperidine (**3**) or a diethyl amine base (**2**), respectively, the calculated OH bond lengths B3LYP/6-31G(d) (1.0085 vs. 1.0097 Å) and the calculated stretching frequencies (3065 cm^{-1} vs. 2968 cm^{-1}) are different. Experimentally this is demonstrated in the tri-chloroderivatives. This difference can possibly be related to differences in base strength as the pK_a values are 11.26 and 11.02, respectively, for piperidine and diethylamine. In that case the difference in OH stretching frequencies can possibly be explained by the differences in the calculated O…N distances, 2.634 vs. 2.640 Å, respectively or it can be related to the solvent reaction field. [15] Steric strain was found to play a role in 3,5,6-trimethyl, dimethyl [16] and in chloro substituted compounds. In the latter caused by interactions with chlorine. [17]

2.4 *NMR spectroscopy*

The ^{13}C NMR spectrum of Cl_4MBde at variable temperature is found in Ref. 18. Based on the given assignment C-1 and C-6 show large and opposite changes with lowering of the temperature. The chemical shift difference between C-2 and C-6 is small, ~1 ppm. It is important to remember as seen from the UV data (Figure 3) that the molecule changes from the M-form towards the PT-form as the temperature is lowered. Judging from the theoretical calculations of ^{13}C nuclear shieldings, using B3LYP/6-31G(d) and the GIAO formalism [19,20] for both the M- and the PT-form, the largest differences are seen for C-1, C-2 and C-4. As the chemical shift of C-2 and C-6 are very close (see Table 2) we suggest an interchange in the assignment of C-2 and C-6.

Table 2. Experimental ^{13}C chemical shifts [18] and ^{13}C calculated nuclear shieldings for Cl_4MBde

Carbon	**Experimental 30 °C**	**Experimental -97 °C**	**Differences**	**Calculated M-form**	**Calculated PT-form**	**Difference**
C-4	119.9	120.6		48.5	59.1	-10.6
C-3	130.0	130.3		39.6	41.5	-1.9
C-2	119.0	118.1		59.4	69.5	-10.1
C-1	156.3	160.3	-4.0	21.3	11.3	10.0
C-6	120.3	114.4	5.9	49.0	44.3	4.7
C-5	131.4	130.9		36.1	33.8	2.3
CH_2	54.7	53.6	1.1	120.9	119.0	1.9
CH_3	46.7	45.5	1.2	137.3	140.4	-3.1
CH_3	10.4	8.7	1.7	140.7	140.6	0.1

2.5 *Deuterium isotope effects on ^{13}C chemical shifts*

A very interesting graph of deuterium isotope effects is seen in Figure 6. [7] With C-2 and C-6 interchanged (see above) large changes are seen for C-1 and C-2 and to some extent C-4 with C-1 and C-2 having opposite signs. The variations are found to be parallel to the difference in chemical shifts for a given carbon in the M- and PT-forms for these molecules (see Table 1).

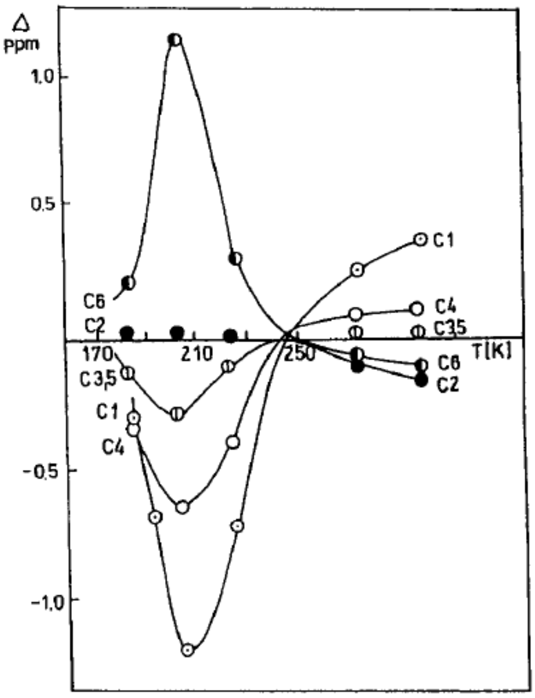


Figure 5. Deuterium isotope effects on ^{13}C chemical shifts of Cl_4MBde (**2**) at variable temperature in CD_2Cl_2. Reproduced from Ref. 7 with permission from Elsevier.

Equilibrium isotope effects can in a simple way be described as in [21] (x is a multiplication sign):

$$\Delta C_{measured} = X_M \text{ x } \Delta C_{int}(M) + (1-X_M)\, \Delta C_{int}(PT) + \Delta X_{H(D)} \text{ x } (\delta C_{M-}\, \delta C_{PT})$$

At room temperature we can assume that the M-form is dominating (see below) giving for C-1 a positive isotope effect. A correlation has been established between the OH bond length and the $^2\Delta$C(OD) isotope effects. [22] Using data from BLYP/6-31G(d) calculations a similar trend can be seen for a series of compounds (methyl salicylate[23], salicylaldehyde [23], 2-hydroxyacetophenone [23], 2-hydroxy-4-methoxyacetophenone [23], 1,3,5-triacetyl-2,4,6-trihydroxybenzene [22], anthralin [24], 6-methoxy-1,9-dihydroxy-2-acenaphthone [25], 2-hydroxy-thioacetophenone [26],4,6-dimethoxy-2-hydroxy-thioacetophenone [26]) (Figure 6, Series 1). Series 2 represents data for Mannich bases **2**-5, **7**, **11** and **12** (Taken from Ref. 27.) From this plot an isotope effect for Cl_4MBde (**2**) and for Cl_4MBpip (**3**) of ~0.5 ppm can be estimated. This value is larger than those observed for these compounds in $CDCl_3$, 0.28 and 0.44 ppm [27], and also larger than that estimated (0.38 ppm) from the plot in Figure 6. These findings can be explained by a finding that the equilibrium is already at play at ambient temperature (see below). This feature is seen even more clearly for 2-(N,N-didecylaminomethyl)-4-nitro-5-chloropenol, $^2\Delta$C(OD) = -0.30 ppm and for 2-(N,N-didecylaminomethyl)-4-nitro-3,5-dichloropenol, $^2\Delta$C(OD) = -0.45 ppm.

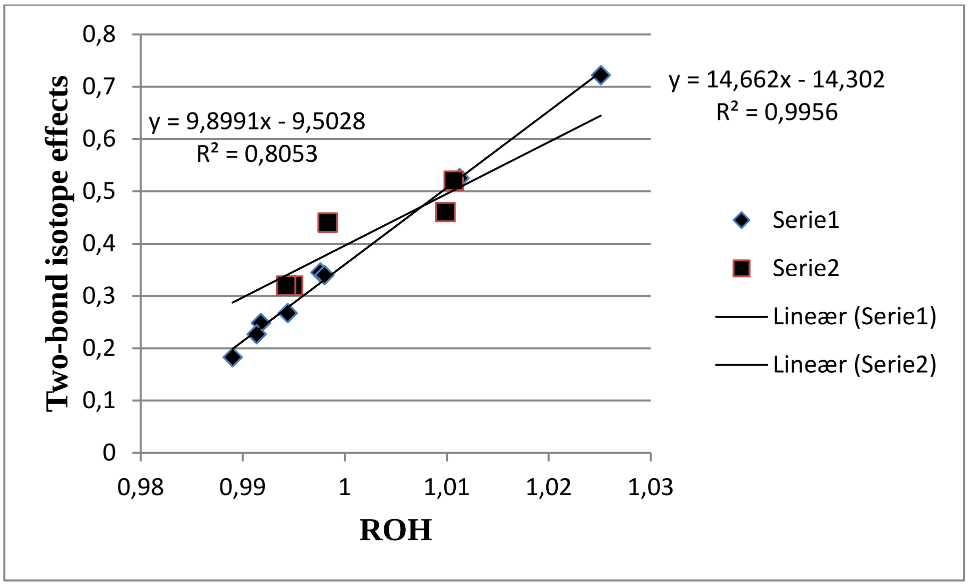


Figure 6. Experimental two- bond deuterium isotope effects from Figure 5 vs. calculated OH bond lengths (B3LYP/6-31G(d) (Series 1 and Series 2, see text).

As the temperature is lowered the equilibrium contribution is increasing. For cases in which the equilibrium isotope effect is dominating, the isotope effects for two carbons may be plotted against each other as seen in [28] (x is a multiplication sign) :

$$\Delta C2_{\text{measured}} = \Delta R_{XH(D)} \text{ x } \delta C2/\,\delta R_{XH} + \Delta X_{H(D)} \text{ x } (\delta C2_{M-}\ \delta C3_{PT})$$

$$\Delta C1_{\text{measured}} = \Delta R_{XH(D)} \text{ x } \delta C1/\,\delta R_{XH} + \Delta X_{H(D)} \text{ x } (\delta C1_{M-}\ \delta C1_{PT})$$

$$\Delta C2_{\text{measured}}/\ \Delta C1_{\text{measured}} = (\delta C2_{M} - \delta C2_{PT})/(\delta C1_{M} - \delta C1_{PT})$$

This should lead to a straight line as is found for temperatures below –23 ^{o}C (Series 2) in Figure 6.

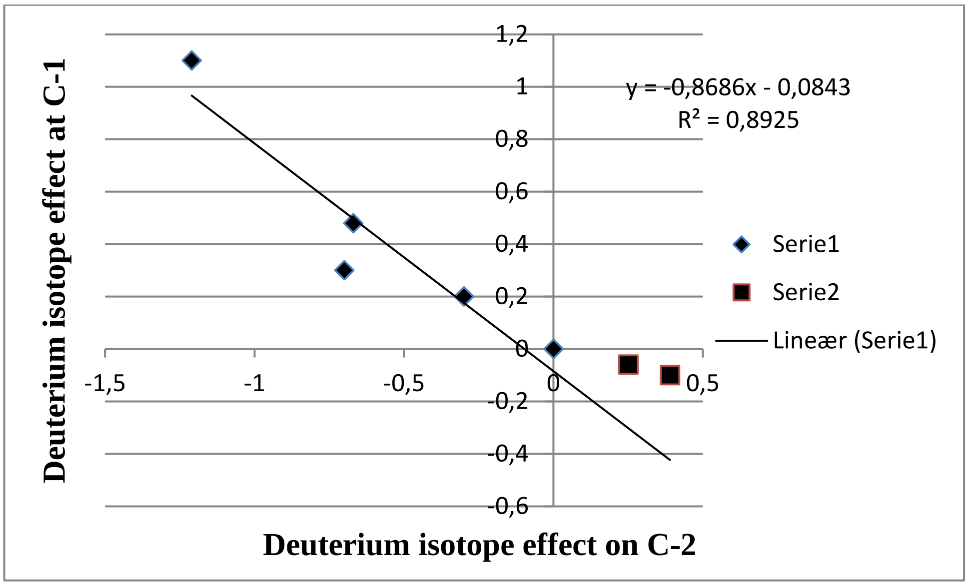


Figure 7 . Plot of deuterium isotope effects for C-2/ C-1 at different temperatures (data from Figure 5).

Furthermore, the signs should depend on the chemical shift difference between the M-and the PT-form. This is also found to be true. For C-4 a similar picture is seen although with smaller isotope effects. The trends of Figure 6 can be explained primarily as a result of equilibrium isotope effects.

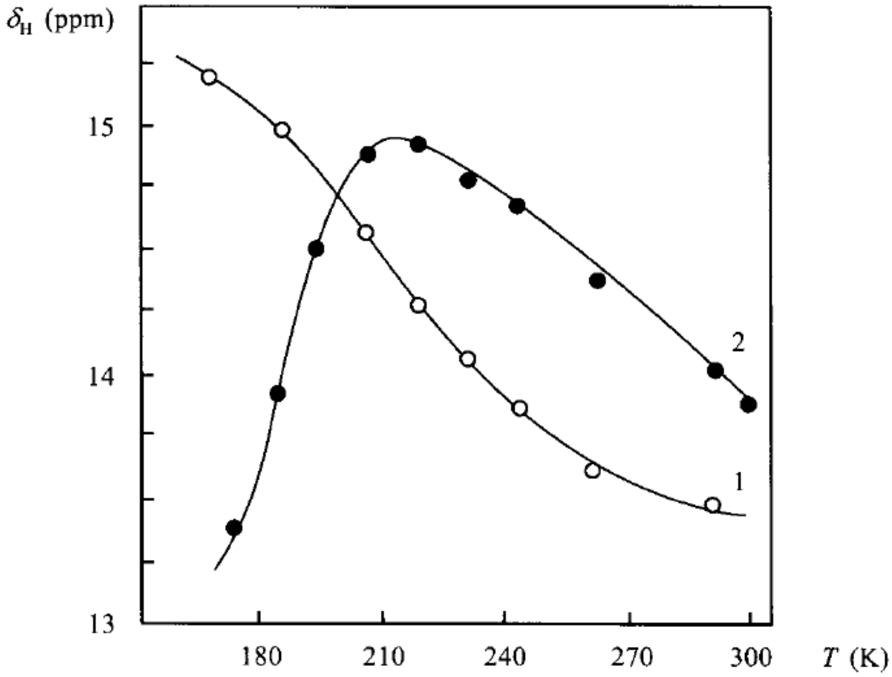


Figure 8. Variation in XH chemical shifts. Closed symbols are for Cl_4MBde (**2**), open symbols for Cl_3MBde (**4**). (From Ref. 3 with permission from ??)

Figure 8 shows how the XH chemical shifts vary with temperature. [18] It is obvious that the geometry of the hydrogen bond changes with temperature, leading to a strengthening as temperature is lowered before for Cl_4MBde tautomerism starts dominating.

3. Conclusions

Cl_4MB derivatives show a rather strong hydrogen bond in the M-form despite the fact that the OH group is twisted 15^o out of the ring plane. The asymmetry of the hydrogen bond potential is described by the isotope ratio for the stretching frequency of 1.33. At ambient temperature Cl_4MB is at the M-form but as the temperature is lowered, tautomerism sets in as judged from the UV spectrum and from the deuterium isotope effects on ^{13}C chemical shifts. Intrinsic deuterium isotope effects over two bonds can be estimated based on calculated OH bond lengths. Simple B3LYP/ 6-31G(d) calculations are used to predict OH stretching frequencies. Using higher basis sets do not lead to an improvement in the predictions.

4. Experimental

4.1 *Calculations*

Molecular equilibrium geometries and harmonic OH stretching wavenumbers have been calculated for the compounds **1 – 11** listed in Table 1, using B3LYP [13] density functional theory (DFT) and the basis sets 6-31G(d) [29] and cc-pVTZ [30]. ^{13}C nuclear shieldings were calculated using B3LYP/6-31G(d) and the GIAO formalism [19,20]. All calculations were performed with the Gaussian 09 software package [29].

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