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Is there an intramolecular hydrogen bond in 2-halophenols?

A theoretical and spectroscopic investigation.

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Abstract:

The Abraham solute hydrogen bond acidity parameter **A** can be derived both from physical methods, **A**(Gen) and NMR experiments, **A**(NMR) and results for a large number of hydroxylic solutes show that the two methods agreed very well. However for halophenols the values of **A**(NMR) were not consistent with the **A**(Gen) values. The values of **A**(NMR) suggest that there is no intra-molecular hydrogen bonding in any of the 2-halophenols. In contrast the values of **A**(Gen)indicate that there is no intra-molecular hydrogen bonding in 2-fluorophenol, but weak intra-molecular hydrogen bonding in 2-chloro, 2-bromo, and 2-iodo-phenol. In view of this uncertainty in the presence or absence of intra-

molecular H-bonds in the 2-halophenols, a detailed investigation of the methods used in the literature is presented together with a novel NMR method to determine the ratio of *cis* and *trans* forms in these compounds. The experimental data is complemented by a detailed theoretical analysis of the structures and bonding in these molecules to assess the presence or absence of an intra-molecular H-bond. We conclude that there is weak hydrogen bonding in 2-chloro, 2-bromo and 2-iodophenol but very little in 2-fluorophenol.

Introduction

The conformations of the 2-halophenols have been the subject of considerable theoretical and experimental investigations[1-14] following Pauling's hypothesis[2] that the two bands observed in the near IR spectra of the 2-chloro, 2-bromo and 2-iodo-phenols were due to the existence of *cis* and *trans* conformers (Fig. 1). Although 2-fluorophenol shows only one band in the near IR spectrum it was suggested[14] that the two bands due to the *cis* and *trans* forms overlap in this spectrum. However, there is still no general agreement on the percent of the two conformers of 2-halophenols in the gas phase or solution, and whether this is due to intra-molecular hydrogen bonding.

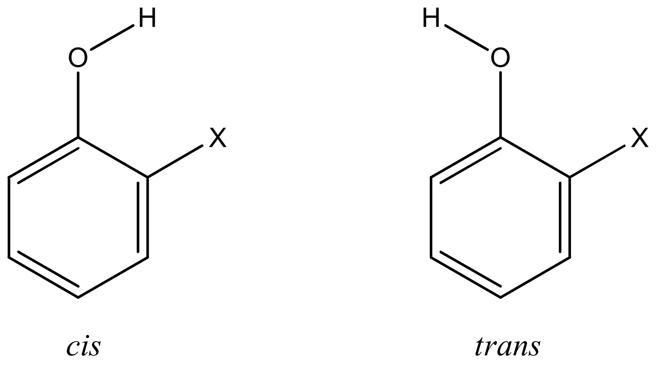

Figure 1. *Cis* and *trans* conformers of 2-substituted phenol.

Recently it has been shown that the difference in the ^{1}H NMR chemical shift of a protic hydrogen in DMSO and $CDCl_3$ solvents is directly related to the overall, or summation, hydrogen bond acidity for a wide range of solutes[15]. This provides a new and direct method of measuring the hydrogen bond acidity. For 54 compounds, the observed shifts for 72 protic hydrogens could be correlated to the Abraham solute hydrogen bond acidity parameter **A**, with a correlation coefficient squared, R^2, of 0.938 and a standard deviation, SD of 0.054 units in **A**. Unlike any previous method for the determination of solute hydrogen bond acidities, the NMR method allows the determination of **A**-values for individual protic hydrogens in multifunctional solutes.

Subsequently it was shown that the NMR **A-**value can be used as a quantitative assessment of intramolecular hydrogen bonding[16]. For hydroxy compounds, if **A** > 0.5 then the OH group is not part of an intramolecular hydrogen bond but if **A** < 0.1 then the OH group forms part of an intra-molecular hydrogen bond. The method has considerable advantages over previous methods for the assessment of intra-molecular hydrogen bonding in that the method is very simple and no comparison compounds are needed.

The method that was originally used to determine the hydrogen bond acidity of a solute, **A**, has been set out several times.[17-20] In brief, equations (1) and (2) for the correlation of water-solvent partition coefficients (log P), and gas-solvent partition coefficients (log K) were constructed.

$$\text{Log}\, P = c + e\mathbf{E} + s\mathbf{S} + a\mathbf{A} + b\mathbf{B} + v\mathbf{V} \qquad (1)$$

$$\text{Log}\, K = c + e\mathbf{E} + s\mathbf{S} + a\mathbf{A} + b\mathbf{B} + l\mathbf{L} \qquad (2)$$

The independent variables in eqns. (1) and (2) are solute descriptors as follows.[17-20] **E** is the solute excess molar refractivity in units of ($cm^3\ mol^{-1}$)/10, ***S*** is the solute dipolarity / polarizability, **A** and **B** are the overall or summation hydrogen bond acidity and basicity, and **V** is the McGowan characteristic volume in units of ($cm^3\ mol^{-1}$)/100. **L** is the gas-hexadecane partition coefficient at 298 K. The coefficients in eqns. (1) and (2) are obtained by multiple linear regression analysis, and serve to characterize the system under consideration. We shall refer to the hydrogen bond acidity of a solute, **A**, as determined by the general procedure using eqns. (1) and (2) as **A**(Gen).

We have reported results for a large number of hydroxylic solutes [15,16] where the **A** (NMR) values agreed very well with those obtained by the general method. In these reports, we did not compare the two methods for the 2-halophenols, as we were concerned about the concentration dependence of the OH chemical shifts in chloroform. We have now determined the NMR chemical shifts in chloroform at various concentrations in order to obtain the shifts at infinite dilution. The values of **A**(NMR) obtained from these chemical shifts did not always agree with the **A**(Gen) values. The NMR method leads to values of **A**(NMR) of 0.62 for 2-fluorophenol, 0.61 for 2-chlorophenol, 0.63 for 2-bromophenol and 0.67 for 2-iodophenol, as well as 0.63 for phenol itself. Using our previous criteria for intra-molecular hydrogen bonding, [16] we would conclude that there is no intra-molecular hydrogen bonding at all in any of the 2-halophenols. However, the corresponding values of **A**(Gen) are 0.59 for 2-fluorophenol, 0.32 for 2-chlorophenol, 0.35 for 2-bromophenol,0.40 for 2-iodophenol and 0.60 for phenol which indicates no intra-molecular hydrogen bonding in phenol or 2-fluorophenol, and weak intra-molecular hydrogen bonding in 2-chloro, 2-bromo, and 2-iodo-phenol.

In view of this uncertainty in the presence or absence of intra-molecular H-bonds in the 2-halophenols, we have made a detailed investigation of the methods used in the literature together with an independent NMR method to determine the ratio of *cis* and *trans* forms in these compounds and thus to assess the presence or absence of an intra-molecular H-bond. Also a detailed analysis of the wave functions of the *cis* conformers were performed applying the Non-Covalent Interaction (NCI) and Quantum Theory of Atoms in Molecules (QTAIM) topological analyses and also the hyperconjugative interactions were evaluated through Natural Bond Orbital (NBO) analysis to give further information on the existence of intra-molecular hydrogen bonding.

Results

IR Spectroscopy

IR has been used extensively to study the *cis-trans* equilibrium in 2-halophenols. Zumwalt and Badger[1] observed two distinct bands in the near IR spectrum of 2-chlorophenol in the vapour which were assigned to the *cis* and *trans* forms. They determined the conformer energy E_{trans}-E_{cis} as 2.8 kcal mol^{-1} at 450 K, which corresponds to a value for the *cis*/*trans* ratio of 23. They noted that Pauling[2] found the conformer energy to be 1.4 kcal mol $^{-1}$ for CCl_4 solutions at room temperature, which corresponds to a value of 11 for the *cis*/*trans* ratio. Subsequently Baker[3] used very pure samples of the 2-halophenols and obtained much larger *cis*/*trans* ratios for the 2-halophenols: 2-chloro 56, 2-bromo 38 and 2-iodo 13.5, leading to an order of weak intra-molecular hydrogen bonding of Cl >Br>I in solvent CCl_4. Only one band in the near IR region was found for 2-fluorophenol.[3] A summary of these and other IR results was presented by Robinson *et al*[7] who gave ΔE values (kcal mol^{-1}) for the vapour and CCl_4 solution. These were 3.6 ± 0.3 (vapour) and 1.4 ± 0.6 (soln) for 2-chloro; 2.6 ± 0.5 (vapour) and 1.7± 0.4 (soln) for 2-bromo and 3.0 ± 0.3 (vapour) and 1.2± 0.2 (soln) for 2-iodo phenol.

A different IR technique to measure the enthalpies was that of Carlson *et al*[8] who observed the frequency of the OH torsional vibrations in these compounds from which the potential function for internal rotation may be calculated. They obtained values of ΔE (kcal mol^{-1}) of 1.6, 1.6, 1.5, 1.3 (vapour) and 1.4, 1.6, 1.6, 1.5 (cyclohexane) for the 2-fluoro, 2-chloro, 2-bromo and 2-iodo-phenols. These measurements are unusual in that they show no difference in ΔE between the vapour and non-polar solvent for all the compounds, whereas all the other IR results (above) and solvation theory (see later) suggest a change of 1-2 kcal mol^{-1} in ΔE between the vapour and solvent. We note that the ΔE values for the solution obtained here are in good agreement with the other IR results.

NMR Spectroscopy

NMR studies on this equilibrium are made more complex by the rapid rate of inter-conversion of the two conformers which is fast on the NMR time scale so that only one OH peak is observed. The OH chemical shift is a measurable and important quantity, which could in principle, give direct information about the molecular structure. It is however, dependant on any intermolecular hydrogen bonding which in non-polar solvents can only be removed by dilution of the sample.

An early IR and NMR study by Seguin *et al*[21] of a number of substituted phenols at low concentrations in CCl_4 included the 2,6-dichloro and 2,6-difluoro derivatives. They found a correlation between the IR OH frequency with the CNDO/2 calculated OH bond length but the ortho-phenols were exceptions. NMR studies on the 1:1 equilibrium of 2-halophenols against bases in CCl_4 solvent by Salman and Kudier[22] also measured the OH shifts as a function of concentration but only to 0.1 M concentration. They stated there was none, or very little, intra-molecular hydrogen bonding.

More recently Abraham and Mobli[23] noted that the OH chemical shift in phenol increases linearly with concentration in non-polar solvents from 5.36 to 6.98 δ (at 120 mg/ml) in CCl_4 and follows eqn. 3 in $CDCl_3$ where c is the concentration in mg/ml. Thus any measurement of the OH shift at >10 mg/ml (0.1 M) conc. in non-polar solvents will be affected by the intermolecular H-bonding.

$$\delta_{OH} = 4.60+0.01c \qquad (3)$$

We have therefore determined the concentration dependence of the ^1H shifts of the OH proton in the 2-halophenols, 2-methoxyphenol and 2,6-difluorophenol to obtain the ∞ dilution values, see Table 1.

Table 1. The Concentration Dependence of the OH Chemical shift (δ) in o-phenols in $CDCl_3$ and DMSO and the determination of **A**(NMR)*.

Conc. (mM)	$\delta(CDCl_3)$	δ(DMSO)	$\delta\Delta$	**A**(NMR)
		2-Fluorophenol		
2033	5.684	9.725	4.041	0.54
177	5.155	9.725	4.570	0.61
19	5.098	9.725	4.627	0.62
3	5.091	9.725	4.634	0.62
0.9	5.091	9.725	4.634	0.62
		2-Chlorophenol		
1114	5.694	10.083	4.389	0.59

256	5.564	10.083	4.519	0.61
66.6	5.529	10.083	4.554	0.61
11.7	5.519	10.083	4.564	0.61
2.0	5.517	10.083	4.566	0.61
0.4	5.517	10.083	4.566	0.61
2-Bromophenol				
1648	5.676	10.141	4.465	0.64
369	5.533	10.141	4.608	0.62
95	5.497	10.141	4.644	0.62
25.4	5.487	10.141	4.654	0.63
6.0	5.485	10.141	4.656	0.63
1.1	5.484	10.141	4.657	0.63
0.9	5.484	10.141	4.657	0.63
2-Iodophenol				
3141	5.589	10.278	4.689	0.63
571	5.325	10.278	4.953	0.67
124	5.275	10.278	5.003	0.67
24.5	5.263	10.278	5.015	0.67
3.8	5.261	10.278	5.017	0.67
1.1	5.261	10.278	5.017	0.67
0.4	5.261	10.278	5.017	0.67
2-Methoxyphenol				
3667.0	6.251	8.554	2.303	0.31
1107.0	5.811	8.554	2.743	0.37
205.0	5.637	8.554	2.917	0.39
38.0	5.604	8.554	2.950	0.40
9.1	5.597	8.554	2.957	0.40
2.3	5.596	8.554	2.958	0.40
1.1	5.596	8.554	2.958	0.40

26-Difluorophenol				
1631.8	5.235	10.105	4.870	0.65
331.9	5.282	10.105	4.733	0.64
63.5	5.168	10.105	4.847	0.65
12.7	5.143	10.105	4.962	0.67
2.6	5.138	10.105	4.967	0.67
0.95	5.136	10.105	4.879	0.66
0.49	5.136	10.105	4.879	0.66

* This work.

Abraham and Mobli [23] also found that for polar solvents such as DMSO and also for phenols with strong intra-molecular H-bonds (e.g. *o*-nitrophenol) there is no concentration dependence of the OH chemical shift. They calculated the ^{1}H chemical shifts for a number of phenols, including the OH proton, using the CHARGE program[24]. This program calculates ^{1}H chemical shifts based on atomic charges, electric fields, steric and anisotropy effects and now includes all the common functional groups in organic chemistry. The program was extended[23] to the calculation of OH chemical shifts in alcohols and in *ortho* substituted phenols with strong intramolecular H-bonds (e.g. 2-hydroxybenzaldehyde, 2-hydroxy acetophenone, 2-nitrophenol and methyl salicylate) with OH---O distances shorter than 2.0 Å. In the latter compounds the large deshielding effect of the *ortho* substituent on the OH proton was reproduced following *ab initio* calculations by a linear function of the H---O=C distance. The semi-empirical calculations of the OH shifts in phenols were shown to be more accurate than either the *ab initio* (GIAO) or database (ACD) approaches[23].

More recently two papers were presented on the measurement and calculation of OH chemical shifts in phenols[25,26] using the GIAO method[27] of calculating nuclear shifts at the DFT/B3LYP/6-311++G (2d,p) level with the polarisable continuum model (PCM). The OH shifts of three phenols in $CDCl_3$, acetone, acetonitrile and DMSO were calculated. In a subsequent paper, the temperature coefficients of the OH shifts in phenolic acids, flavones etc were also measured and calculated and shown to give an indication of hydrogen bonding in these molecules. Due to the basis set dependence of *ab initio* calculations they are most useful in interpreting known data rather than predicting unknown values and the above papers illustrate this very well.

None of the above investigations considered the isomerism of the 2-halophenols, or calculated the OH chemical shift in *ortho* substituted phenols, but if the OH chemical shifts in the *cis* and *trans* conformers of the 2-halophenols can be calculated and there is an appreciable difference between them, then the observed value of the OH shift will give immediately the proportions of the conformers from eqn 4, where δ_{obs}, δ_{cis} and δ_{trans} are the observed OH shift and the calculated shifts for the *cis* and *trans* conformers and n_{cis} and n_{trans} the populations of the conformers.

$$\delta_{obs} = n_{cis}\,\delta_{cis} + n_{trans}\,\delta_{trans} \qquad (4)$$

$$n_{cis} + n_{trans} = 1$$

In order to extend the CHARGE model to the 2-halophenols it is necessary to reproduce the effect of the 2-substituent on the OH proton in the *cis* isomer. This will include π effects which would be expected to be the same in the *cis* and *trans* forms, and close range steric and electric field effects. The π effects are already calculated within the program which leaves the steric and electric field effects. As there are no other molecules in the data base with an Ar-OH---X steric interaction, this semi-empirical method requires standard molecules for the parameterisation. The most appropriate compounds to use are the 2,6-dihalophenols. They are in a single conformation and have similar interactions to the 2-halophenols. In the CHARGE model, there is a steric interaction between the *ortho* halogen and the *cis* OH in all the *o*-halo-phenols except for the *o*-fluorophenols. It has been shown previously in this model that fluorine does not have a steric effect[24]. The only direct effect the fluorine has on the OH proton chemical shift is due to the electric field of the fluorine atom. The Ar-OH---F interaction is again unique in the data base and thus will also require defining; again the 2,6-difluorophenol is the appropriate model. The iteration process was straightforward and Table 2 shows the observed and calculated OH shifts for some 2,6-dihalophenols and also the calculated shifts for the *cis* and *trans* conformers of the 2-halophenols.

Table 2. Observed vs calculated OH chemical shifts δ (ppm.) in phenols*.

Compounds	$\delta_{calc.}$ (ppm)	$\delta_{obs.}$ (ppm)
Phenol	4.73	4.69[c]
2,6-difluorophenol	5.15	5.14
2,4,6-trifluorophenol	4.93	4.93[d]
2,6-dichlorophenol	5.86	5.89[e]
2,4,6-trichlorophenol	5.72	5.88[e]
2,6-dibromophenol	5.87	5.87[e]
2,4,6-tribromophenol	5.83	5.88[d]
2,6-diiodophenol	5.40	-
2,6-dimethoxyphenol	5.62	5.56[d]
2-fluorophenol	5.35[a], 4.57[b]	5.091
2-chlorophenol	5.85[a], 4.66[b]	5.517
2-bromophenol	5.76[a], 4.76[b]	5.484
2-iodophenol	5.36[a], 4.71[b]	5.261
2-methoxyphenol	5.55[a], 4.41[b]	5.596

*$CDCl_3$ soln., this work, a) *cis* form, b) *trans* form, c) ref 23, d) ref 37, e) ref 38.

The calculated shifts are for $CDCl_3$ solvent as this is the solvent used for the parameterisation. The difference in the calculated OH chemical shift between the *cis* and *trans* isomers is small (0.6-1.1 ppm) thus the calculations depend critically on the accuracy of the observed data. The results in Table 2 indicate that 2-methoxyphenol exists entirely in the *cis* form but the 2-halo-*o*-phenols are mixtures of *cis* and *trans* forms. Using the data in the Table 2 together with eqn 4 gives the percentages of *cis* isomer as 65, 76, 71, 85 and 100 for the 2-fluoro-, 2-chloro-, 2-bromo-, 2-iodo- and 2-methoxy-phenols, respectively. This leads to E_{trans}-E_{cis} values of 0.4, 0.7, 0.5, 1.0 and > 2.0 kcal mol^{-1}, respectively. These results will be considered later.

Dipole moment measurements.

In principle, the observed dipole moments of these compounds should give information on the conformer ratios as the dipole moments of the *cis* and *trans* forms differ. The observed dipole moment is the weighted average of the *cis* and *trans* forms according to eqn 5,

$$\mu_{obs}^2 = n_{cis}\,\mu_{cis}^2 + n_{trans}\,\mu_{trans}^2 \qquad (5)$$

$$1 = n_{cis} + n_{trans}$$

where n_{cis} and n_{trans} are the mole fractions of the *cis* and *trans* forms. McClellan[28] compiled a list of all the dipole moments in the literature from the earliest days (1925) until 1981 and the dipole moments of the 2-halophenols are included in this work. They have been recorded in various solvents; alkanes, CCl_4, benzene and dioxane being the most common, and also in the gas phase. The dipole moments of the individual conformers have not been experimentally determined. However the semi-empirical CHARGE model which was designed to calculate compound electrostatics from the molecular dipole moments[27] does calculate the partial atomic charges in molecules and from these the dipole moments of the conformers. The partial atomic charges are calculated from the atomic electronegativities for saturated compounds and from these plus the π charges for olefinic and aromatic compounds. In the latter case the observed dipole moments for some base molecules were used to check the Huckel calculations. Table 3 gives the observed and calculated dipole moments of the 2- and 4-halophenols.To minimise any medium effects the experimental dipole moments in Table 3 are given for the non-polar solvents listed.

Table 3. Observed* vs calculated dipole moments (Debye) for phenols.

Compounds	$\mu_{calc.}$	$\mu_{obs.}$
Phenol	1.52	1.55^{c}

4-fluorophenol	2.13	2.15[c]
4-chlorophenol	2.23	2.25[c]
4-bromophenol	2.52	2.2[c]
4-iodophenol	2.24	2.21[c]
2-fluorophenol	0.53[a], 2.31[b]	1.16[d]
2-chlorophenol	0.48[a], 2.31[b]	1.15[d], 1.17[e]
2-bromophenol	0.19[a], 2.64[b]	1.10[d]
2-iodophenol	0.51[a], 2.34[b]	1.25[e]

* ref 28; a) *cis* form; b) *trans* form; c) benzene solvent; d) CCl_4 solvent; e) decalin, cyclohexane solvent.

We exclude benzene from the 2-halophenols results as this solvent behaves anomalously in such conformational equilibria,[29] and also more polar solvents such as dioxane which give increased values of the dipole moments. For example, the dipole moments of phenol, 2-fluorophenol and 4-fluorophenol in dioxane are 1.84, 1.84 and 2.67 D, respectively. If only the 2-fluorophenol measurement was considered it could be suggested that the increased value of the dipole moment was due to a greater percentage of the more polar *trans* conformer in this more polar solvent. However, the same increase is observed in both phenol and 4-fluorophenol which are both in one conformation, thus the increase is solely a function of the solvent.

The good agreement of the observed vs calculated dipole moments of the 4-halophenols in Table 3 supports the use of the calculated dipole moments of the *cis* and *trans* conformers of the 2-halophenols to obtain the conformer ratios from the observed dipole moments in eqn. 5. This gives the populations of the *cis* conformer of the 2-halophenols in non-polar media as 79, 79, 83 and 67 % for the fluoro-, chloro-, bromo- and iodo-phenols respectively, which translates into energy differences E_{trans}-E_{cis} of 0.79, 0.79, 0.95 and 0.65 kcal mol^{-1} respectively. The dipole moments (Debye) from our *ab initio* calculations (below) are for the *cis* and *trans* conformers 1.16 and 3.00 (F), 1.27 and 3.11 (Cl), 1.33 and 3.18 (Br) and 1.34 and 3.08 (I). They are larger than the observed values which is usually the case for split basis sets.

Microwave Spectroscopy/Electron Diffraction

A microwave study by Dutta et al[32] observed only transitions due to the *cis* conformer in 2-fluorophenol but noted that due to the poor signal to noise there could be up to 20 % of the *trans* form. Also Vadja and Hargittai[33] in an electron diffraction study stated "a second form of 2-fluorophenol not allowing an OH---F interaction seems to be present in the vapour".

Theoretical data

A theoretical study of F---H-O hydrogen bonding in 2-fluorophenol, 2,6-difluorophenol and 2,3,5,6-tetrafluorohydroquinone[30] at the MP2/6-31G** level gave the conformer energy E_{trans}-E_{cis} for the 2-fluorophenol as 3.0 kcal mol^{-1} and found that the calculated hydrogen bonds shortened in the order 2-fluorophenol > 2,6-diflluorophenol > 2,3,5,6-tetrafluorohydroquinone. The calculations suggested weak hydrogen bonding between the OH and F atoms. Mobli[31] calculated E_{trans}-E_{cis} for a number of 2-substituted phenols with the DFT method at the B3LYP/6-311++G (d,p) level and obtained the results in Table 5 for the 2-halophenols. He also obtained the values for 2-methylphenol of -0.80, 2-methoxyphenol 5.40, 2-cyanophenol 2.45 and 2-trifluoromethylphenol 1.73 kcal mol^{-1}. Our calculations at the MP2/aug-cc-pVTZ level gave ΔG values for all the 2-halophenols, including the iodophenol (table 5) and also for 2-methoxyphenol (4.3 kcal mol^{-1}).

Table 4. Calculated Solvation Energy Difference Δ (Ev-Es) between *trans-cis* for 2-halophenols.

Solvent	ε	F	Cl	Br	I
Hexane	1.89	0.47	0.42	0.45	0.33
CCl_4	2.24	0.59	0.52	0.56	0.41
Et_2O	4.34	0.97	0.89	0.97	0.70

$CHCl_3$	4.81	1.02	0.95	1.02	0.74
Acetone	21.2	1.54	1.44	1.68	1.14
CH_3CN	37.5	1.72	1.60	1.76	1.26
DMSO	46.6	1.80	1.68	1.83	1.33

Table 5. Observed vs calculated conformer energy differences ΔG (*trans-cis)* in 2-halophenols.

	Vapour		Solvent
Compounds	Calc.	Obs.	Obs.
2-fluorophenol	3.0[a], 3.9[b] ,2.5[k]	1.6[c], 0.5[j]	0.7[g], 1.4[d], 0.4[e]
2-chlorophenol	4.3[a],3.2[k]	1.6[c],3.6[f]	0.8[g], 1.6[d], 0.7[e], 1.4[h]
2-bromophenol	4.6[a],3.4[k]	1.5[c],2.6 [f]	0.8[g], 1.6[d], 0.5[e], 1.7[h]
2-iodophenol	3.7[k]	1.3,[c] 3.0[k]	0.4,[g] 1.5,[d] 1.0,[e] 1.2[h]

a) ref 31, b) ref 30, c) ref 8, d) ref 8,cyclohexane soln., e) nmr, $CDCl_3$ soln. this work, f) ref 7, g) dipole moments, CCl_4 soln. this work, h) ref 7, CCl_4 soln, j) ref 33, k) ΔG values obtained in this work at the MP2/aug-cc-pVTZ level.

Discussion

The observed conformer energies obtained from the various techniques are given in Table 5. It is of interest to compare the observed and calculated conformer energies. In order to calculate the conformer energies in solution the solvation energy of each conformer must be added to the calculated vapour phase energy. The solvation energies were calculated using the MODELS program[34] which is based on the Onsager theory[35] and includes both the dipolar and quadrupolar reaction fields to calculate the solvation energy. It has been used to calculate the solvent effects in a variety of conformational equilibria.[29,34] The solvation energies for a number of solvents are given in Table 4. Note that the solvation energy is *negative*. The *trans* conformer is stabilised with respect to the *cis* conformer due to the increased solvation energy of the more polar *trans* form. This stabilisation is *ca* 0.5 kcal mol^{-1} in non-polar solvents (hydrocarbons, CCl_4), 1.0 kcal mol^{-1} in chloroform and 1.5-2.0 kcal mol^{-1} in DMSO, with as expected the largest values for the 2-fluorophenol and lowest for the 2-iodophenol. Note that the calculations are solely due to the reaction field of the solute, and do not take account of any intermolecular H-bonding with the solvent. The results of these calculations for any solvent when added to the calculated *ab initio* vapour state energies give the calculated energies for that solvent.

The data in Tables 4 and 5 can now be used to compare the observed and calculated values of the conformer energy differences in the 2-halophenols in the various media. If we consider first the vapour phase values, there is some doubt about the values in ref. 8 as this investigation obtained the same values for the vapour and for cyclohexane solution, which is questionable. If we weight these values appropriately then the most likely values of E_{trans}-E_{cis} for the vapour are 1.0, 3.0, 2.6, 2.6 kcal mol^{-1} for the 2-fluoro, 2-chloro, 2-bromo and 2-iodo, respectively. The value for the 2-fluoro is the most uncertain as the microwave[32] and electron diffraction[33] experiments only suggested the existence of a second (*trans*) conformer without any measurements. It is however clear from the data in Table 5 that the theoretical calculations give much larger values of the conformer energies than the experimental values in every case.

There are more experimental values in the condensed phase and these are also of interest. In view of the results in Table 4 it is necessary to consider the solvent used together with these values. For 2-fluorophenol the values are 0.7 (CCl_4), 1.4 (cyclohexane) and 0.4 ($CDCl_3$). Table 4 shows the solvation energy difference for the two non-polar solvents is very small but between these solvents and chloroform it is 0.5 kcal mol^{-1}. This is in good agreement with the experimental data. Thus for 2-fluorophenol these results suggest E_{trans}-E_{cis} is 1.5 kcal mol^{-1} in the vapour decreasing to 1.0 kcal mol^{-1} in non-polar solvents and 0.5 kcal mol^{-1} in $CDCl_3$.

For 2-chlorophenol the values in Table 5 are 0.8 (CCl_4), 1.6 (cyclohexane), 1.4 (CCl_4) and 0.7 ($CDCl_3$). Using the calculated solvation energies and averaging these results gives E_{trans}-E_{cis} values of 1.9 (vapour), 1.5 (cyclohexane), 1.4 (CCl_4) and 1.0 ($CDCl_3$). The data in Table 5 for the 2-bromo and

2-iodophenols are very similar to that for the 2-chlorophenol. The dipole moment value is again low but the other three values consistent. The same reasoning gives for the 2-bromo (E_{trans}-E_{cis}) equal to 2.1 (vapour), 1.6 (cyclohexane), 1.5 (CCl_4), 1.1 ($CDCl_3$), and for the 2-iodo (E_{trans}-E_{cis}) equal to 1.7 (vapour), 1.4 (cyclohexane), 1.3 (CCl_4), 1.0 ($CDCl_3$).

The extrapolated values for the conformer vapour state energy differences E_{trans}-E_{cis} from the condensed phase measurements plus reaction field theory are 1.5, 1.9, 2.1, 1.7 kcal mol^{-1} for the 2-fluoro, 2-chloro, 2-bromo and 2-iodo phenols respectively. These differ from the experimental vapour state conformer energies above of 1.0, 3.0, 2.6, 2.6 kcal mol^{-1} for the 2-fluoro, 2-chloro, 2-bromo and 2-iodo respectively but they show a similar pattern. The 2-fluoro has the lowest value, the 2-chloro and 2-bromo are very similar, and the 2-iodo is slightly less. These can now be compared with our most recent calculated values of ΔG (Table 5) of 2.5, 3.2, 3.4, 3.7 kcal mol^{-1}. We note that the more advanced the quantum mechanical calculation, the lower is the *trans-cis* energy difference. Even so, it is clear that the calculated values are still much larger than the observed values. Interestingly a related conclusion was observed recently in an analysis of F---H-N interactions in 2-fluorobenzamide[36]. Again the *ab initio* calculations considerably over emphasised the attractive F---H interaction.

The energy difference between the *cis* and *trans* conformers is an indication of possible hydrogen bonding but the wave function of the molecule can also provide important information. The optimized wave-functions (matrix density) for the *cis* conformers of the fluoro, chloro and bromo phenols were analysed according to topological theory of Non-Covalent Interactions (NCI) using NCIPLOT [39] and the Quantum Theory of Atoms in Molecules (QTAIM) from the AIMAL program.[40] . The hyperconjugative interactions were evaluated through the Natural BondOrbital (NBO) approach to determine which interactions are involved in the O-H---X molecular fragment. The basis set used for iodine is very different[41,42] which makes such comparisons less rigorous.

The NCI topological analysis was applied using the NCIPLOT program[43]. The NCI isosurface (Fig. 2) and the plot of the reduced density gradient (RDG) *versus* sign (λ_2)ρ (Fig. 3) are shown for the *cis* conformers. The blue-red colours in the gradient isosurfaces (Fig. 2) are obtained according to the corresponding values of sign (λ_2)ρ, which can be used to assess the strength of the interactions.[43]

As can be seen from Figure 3, there is one negative value of sign (λ2)ρ, which indicates an attractive interaction (blue colour) between O-H and halogen and oxygen for 2-methoxyphenol. The positive values of sign (λ2)ρ (Fig. 3) indicate nonbonding overlap between O-H and the halogen and oxygen and are shown in red in the NCI isosurface (Fig. 2). It can also be observed from the NCI isosurface that the attractive interaction increases from F to Br derivatives and that the attractive interaction (blue colour) for the OMe group is more similar to Cl than F, this can be stated because all the figures are obtained using the same parameters.

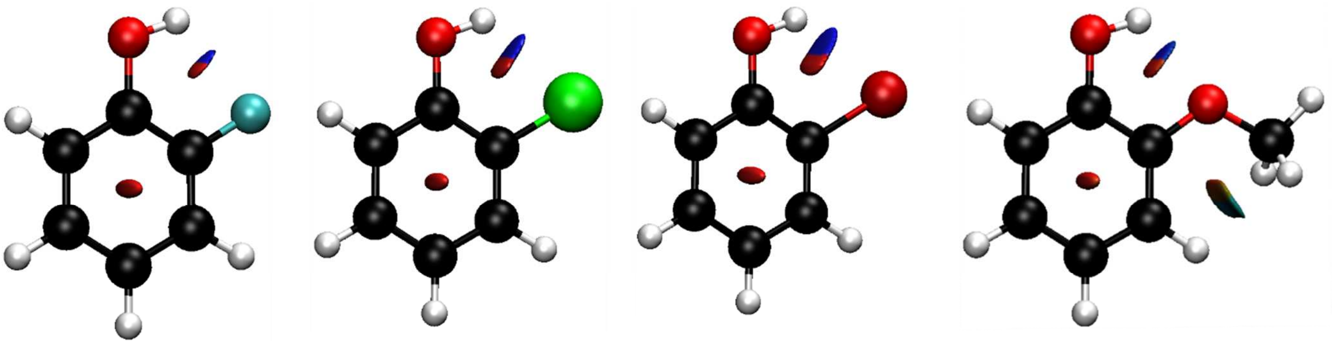

Figure 2. NCI isosurface for the *cis* isomers of the 2-fluorophenol, 2-chlorophenol, 2-bromophenol and 2-methoxyphenol, respectively.

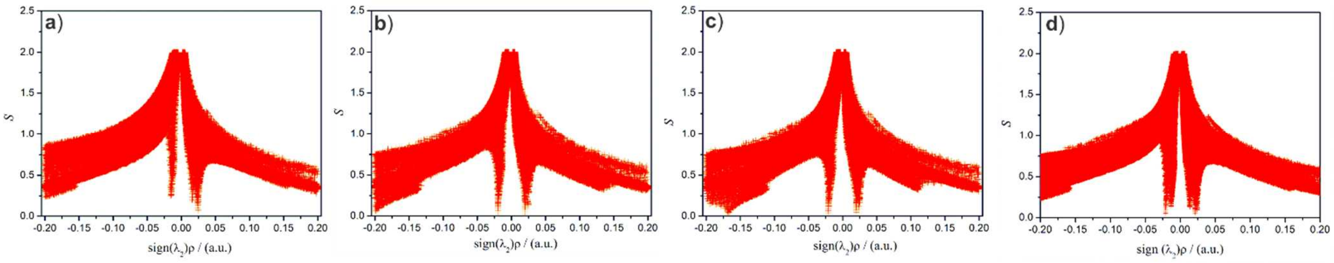

Figure 3. Plot of the reduced density gradient (RDG) *S* and sign (λ_2)ρ: **a**) 2-fluorophenol; **b**) 2-chlorophenol, **c**) 2-bromophenol and **d)** 2-methoxyphenol.

The attractive interactions shown on the RDG plot for 2-fluorophenol (Fig. 3a) do not reach the zero value, suggesting that there is no bond critical point (BCP) between O-H---F in the QTAIM analysis which can be used to detect an intramolecular hydrogen bond between O-H---F. However, the RDG does reach zero for 2-chloro- and 2-bromo-phenols (Fig. 3b and 3c), suggesting a BCP in the QTAIM analysis and the occurrence of an intramolecular hydrogen bond. The RDG plot (Fig. 3) for 2-methoxyphenol is also more similar to 2-chloro-phenol than 2-fluoro-phenol in agreement with the NCI plots (Fig. 2).

The same wave-functions for the *cis* conformers were analysed using the QTAIM approach and the results are shown in Figure 4. There is a BCP between the hydrogen of the O-H group and the chlorine and bromine atoms, but not for fluorine, suggesting that an intramolecular hydrogen bond occurs only for the chloro and bromo derivatives, supporting the NCI results. While NCI topological analysis suggests that 2-methoxyphenol is more similar to 2-chloro- and 2-bromo-phenol the QTAIM analysis suggests a similarity with 2-fluorophenol, because there is no BCP between O-H and the O in the QTAIM topological analysis for 2-methoxyphenol (Fig. 4). This behaviour probably occurs because we are working on a borderline between both methodologies and it is difficult to distinguish small variations in electronic environment.

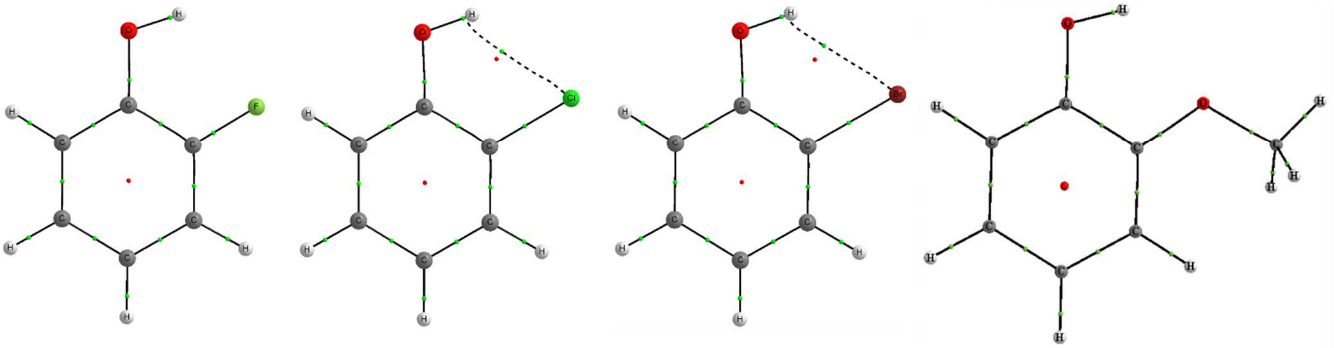

Figure 4. QTAIM molecular graphics for the *cis* conformers of 2-fluoro-, 2-chloro-, 2-bromo- and 2-methoxy-phenols.

The NBO analysis gives us the delocalisation interaction energy between the lone pair of halogen LP(X) and the sigma antibonding O-H orbital ($\sigma^*_{O\text{-}H}$), as it is known that halogens possess three lone pairs, LP(1), LP(2) and LP(3). Only LP(2) has the symmetry to interact with the $\sigma^*_{O\text{-}H}$

orbital. The delocalisation interaction energy between LP2(X) → $\sigma^*_{O\text{-}H}$ is 0.7, 2.8, 3.9 kcal mol^{-1} for 2-fluoro-, 2-chloro- and 2-bromo-phenols, respectively. The energy for the fluoro derivative is very small in comparison with the other compounds. For 2-methoxyphenol LP2(O) does not have the correct symmetry to interact with the $\sigma^*_{O\text{-}H}$ orbital. LP2(O) in phenols has the correct symmetry to interact with the π system of the benzene ring, which is the reason for the OH group in phenol acting as an electron-donating group. For 2-methoxyphenol only LP1(O) has the correct symmetry to interact with the $\sigma^*_{O\text{-}H}$ orbital, but it is also known that LP1(O) is much deeper in energy than LP2(O), thus the interaction is less efficient leading to a calculated value from NBO analysis for LP1(O)→$\sigma^*_{O\text{-}H}$ equal to 1.35 kcal mol^{-1} at the applied level of theory. The value for LP1(O)→$\sigma^*_{O\text{-}H}$ delocalization energy for 2-methoxyphenol is more similar to the value observed for 2-fluorophenol than for 2-chlorophenol which corroborates the absence of BCP in the QTAIM analyses.

The OH bond length has also been used to detect hydrogen bonds. The calculated bond length for the *trans* conformer is 0.964 Å in all the compounds whereas in the *cis* conformer it is 0.966 (F), 0.968 (O), 0.969 (Cl), and 0.970 (Br) again supporting the previous results. In a similar manner the OH---X distance is a useful indicator. It is 2.220 Å for 2-fluorophenol, 2.395 (Cl), 2.483 (Br), 2.602 (I) and 2.074 (OMe). The value for the 2-methoxy phenol in which there is an intramolecular hydrogen bond is much less than in the 2-fluorophenol, a good illustration of the difference between oxygen and fluorine.

Finally although the calculated atomic charges depend on the calculations, they can be used to compare the electrostatic interaction between O-H---X (X=F, Cl, Br, O). The atomic charges obtained for X=F, Cl, Br and O are -0.347,-0.007, 0.070 and -0.555 eu from the NBO analysis and -0.159,-0.091,-0.087 and -0.215 eu (charge). In both cases, there is a much larger electrostatic interaction between H---O and H---F than H---Cl or H—Br, suggesting that the electrostatic contribution to intramolecular hydrogen bonding is more pronounced for 2-fluoro- and 2-methoxyphenol than the other halogens.

Conclusions

Studies of the near IR spectra of the 2-halophenols, the CHARGE calculations of NMR chemical shifts and dipole moment calculations all show large values of the *cis/trans* ratio for 2-chloro, 2-bromo- and 2-iodo-phenol in the gas phase and in nonpolar solvents. Calculations on the solvation energies of the two isomeric forms, Table 4, show that the *trans* isomers become more stable by comparison to the *cis* isomers in polar solvents, so that in solvents such as acetonitrile and DMSO the *trans* conformer may predominate. Intra-molecular hydrogen bonding cannot be present in the *trans* forms, so that the proportion of the phenol that is intra-molecularly hydrogen bonded must be reduced in polar solvents. Of course, it does not follow that intra-molecular hydrogen bonding must be present in the *cis* form in any case. This is clearly illustrated by the A(NMR) value for 2,6-difluorophenol of 0.66 (table 1) which is the same as that for 2-fluorophenol. There must always be a cis OH..F interaction in 2,6-difluorophenol yet the **A**(NMR) value is characteristic of no hydrogen bond.

Our theoretical analysis shows that there is no intra-molecular hydrogen bond in cis 2-fluorophenol. This agrees with the results from **A** (NMR) and **A** (Gen) which both indicate there is no intramolecular hydrogen-bond in 2-fluorophenol. Our analysis shows also that there is an intramolecular hydrogen-bond in the *cis* isomers of 2-chlorophenol and 2-bromophenol, but that this is only a weak hydrogen-bond, and not a strong hydrogen-bond. The values of **A** (Gen) and **A** (NMR) for 2-chloro-, 2-bromo- and 2-iodo-phenol also show the absence of a strong-hydrogen bond. The **A**(NMR) results for these three phenols indicate that there is no intramolecular hydrogen-bond at all, but the **A**(Gen) values suggest that there is a weak hydrogen-bond in 2-chloro-, 2-bromo- and 2-iodo-phenol. It is unusual for intra-molecular hydrogen bonding to involve a five-membered ring, as in the cis isomers of the 2-halophenols, but this cannot be the cause of the (not very large) discrepancy. We have determined the OH chemical shifts of 2-chloroethanol in DMSO (δ= 4.934) and the infinite dilution value in $CDCl_3$ (δ = 1.978) to give **A**(NMR) = 0.40, in good agreement with **A**(Gen) of 0.39, and with both **A**(NMR) and **A**(Gen) for 2-methoxyphenol at 0.40 and 0.26 respectively. Both sets of results show weak intra-molecular hydrogen bonding.

Experimental

The determination of NMR chemical shifts was carried out as described previously[36].

Computational

In every case the molecules were planar to give the *cis* and *trans* conformers. For each conformer the C2-C1-O-H dihedral angle was arranged in *cis* and *trans* forms and the geometries were then fully optimized at the MP2 level of theory available in the Gaussian 09 program for C, H, O, F, Cl, Br atoms and the aug-cc-pVTZ basis set was applied, while for iodine an all electron WTBS basis set was used.[39,40] All calculations included the zero-point energy (ZPE) corrections.

Hyperconjugative interactions were evaluated using Natural Bond Orbital (NBO 5.0) analysis as implemented in Gaussian 09, and the calculations were performed at the B3LYP/aug-cc-pVTZ level. QTAIM and NCI topological analyses were performed using the resulting wave functions obtained from the MP2/aug-cc-pVTZ optimizations. QTAIM and NCI topological analyses were carried out with the AIMALL[40,41] and NCIPLOT[39,42,43] programs, respectively.

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