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The effect of intramolecular interactions on hydrogen bond acidity †

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DFT calculations on a range of molecules containing intramolecular hydrogen bonds are reported, with a view to establishing how intramolecular hydrogen bonding affects their intermolecular interactions. It is shown that properties such as the energy of the intramolecular H-bond are unrelated to the ability to form external H-bonds. Conversely, several properties of complexes with a reference base correlate well with an experimental scale of H-bond acidity, and accurate predictive models are determined. A more detailed study, using electrostatic and overlap properties of complexes with a reference base, is used to predict the location, as well as strength, of hydrogen bond acidity. The effects of intramolecular hydrogen bonding on acidity can be seen not just on O–H and N–H, where acidity is greatly reduced, but also on certain C–H groups, which in some cases become the primary source of acidity.

Introduction

The importance of hydrogen bonding extends throughout biological and chemical systems.[1] The highly significant role that intermolecular hydrogen bonding plays in solvation,[2] diffusion into biological tissues or membranes,[3] adsorption on to surfaces[4] and environmental fate[5] are well recognised. They are also crucial in maintaining the shapes of macromolecules such as polysaccharides and the secondary and tertiary structures of proteins. Molecular recognition is often dependent on hydrogen bond formation due to the strong directional preference of these interactions and their relative strength compared to pure van der Waals forces.[6] Intramolecular hydrogen bonds, though often weaker than their intermolecular counterparts, have significant influence on properties such as charge distribution within molecules, the relative stability of conformers and reactivity. Hydrogen bonding can also play a role in biological electron transfer[7] and radical scavenging.[8] Intramolecular hydrogen bonding in catechol-containing benzo-γ-pyrone derivatives (flavonoids) confers higher stability to their radical form and aids electron delocalisation.

The importance of hydrogen bonding has led to the establishment of several experimental scales of H-bonding acidity and basicity, donor and acceptor ability. Following Taft's initial work,[9] general scales based on equilibrium constants for complexation of acids with a reference base (denoted A, or $\Sigma\alpha_2^H$) or bases with a reference acid (B, or $\Sigma\beta_2^H$) were developed by Abraham and co-workers.[10,11] These H-bonding scales may be combined with size and general polarity terms in a linear free energy relation (LFER) approach to modelling solvent–solute interactions, reducing properties such as partition coefficients or biological transport properties to the sum of specific interaction terms.

We have recently demonstrated that values of A and B can be accurately estimated from DFT calculations.[12] Electrostatic potentials, bond critical point (CP) properties and stabilisation energies of complexes of acids with a reference base (NCH was chosen for speed) are found to correlate closely with experimental values of A, while similar models of B were found using base ··· HF complexes. More recently, predictions for multifunctional acids have been made using a combination of electrostatic potential maxima on the van der Waals surface and the energy density calculated at bond CP's of 1 : 1 complexes with NCH.[13] This method not only provides a more robust correlation with experimental A values, but also allows detailed analysis of the individual sites from which acidity arises.

It is anticipated that an intramolecular H-bond will appropriate a considerable proportion of a donor-hydrogen's acidity and therefore the extent to which it can interact with an external base will be reduced. This will then have a marked effect on solvation and related properties. A detailed study of the lipophilicity of *ortho*-substituted phenols[14] suggested that H-bond acidity is dramatically and consistently reduced, while basicity appears to remain largely unaffected. It is our goal here to use the theoretical methods outlined above to study these phenomena in more depth, exploring the source of H-bond acidity in such compounds, as well as testing the performance of previously developed models for these more complex systems.

Calculation methods

We initially collated a total of 11 *ortho*-substituted phenols containing an intramolecular H-bond, all of which have measured H-bond acidities obtained *via* the methods outlined in Ref. 10. All calculations were performed using GAUSSIAN98[15] running on a Compaq XP1000 workstation. Following previous work,[13] geometry optimisations of both the isolated molecules and their corresponding complexes were carried out at the B3LYP/6-31+G(d,p) level.[16,17] For the purposes of comparison, several related molecules not containing an intramolecular H-bond were studied with the same theoretical methods. Since the calculations performed here use a slightly better level of theory than was possible in Ref. 12, the relations between A and calculated properties developed therein were re-trained at this higher level. The results of this re-training differ only slightly from those previously published, and are reported as electronic supplementary information.† However, it is notable that this improvement in theoretical level does not give noticeably better correlations.

The reduction in hydrogen bond acidity, ΔA, due to intramolecular H-bonding was defined as the difference between the experimental value of A and that expected from the inherent polarity of the donor H, calculated as in Ref. 12 from the electrostatic potential at the H nucleus. Interestingly, there appears to be no consensus on how to calculate the strength of an intramolecular H-bond using theoretical means. We have

† Electronic supplementary information (ESI) available: summary of retrained regression using DFT methods. See http://www.rsc.org/suppdata/ob/b3/b300598d/

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Table 1 Calculated properties of acids with intramolecular hydrogen bonds

Compound	Expt A	ΔA	EP_{NUC} (au)	H-bond energy/kJ mol^{-1}		ρ_{CP} (au)
				Isodesmic	*ortho*/*para*	
Catechol	0.88	0.31	−0.975	2.41	10.14	0.017
2-Hydroxyanisole	0.26	0.25	−0.978	4.65	11.92	0.019
2-Chlorophenol	0.32	0.30	−0.960	3.25	6.08	0.017
Salicylic acid	0.72	0.65	−0.965	28.60	23.04	0.042
Salicylaldehyde	0.11	0.44	−0.971	32.87	32.87	0.042
2-Hydroxyacetophenone	0.13	0.37	−0.981	34.50	29.05	0.050
Methyl 2-hydroxybenzoate	0.04	0.46	−0.980	28.77	23.77	0.043
2-Nitrophenol	0.05	0.60	−0.954	20.06	14.56	0.047
2,4-Dinitrophenol	0.09	0.70	−0.928	25.34	[a]	0.047
2,5-Dinitrophenol	0.11	0.66	−0.933	16.68	[a]	0.046
2,6-Dinitrophenol	0.17	0.61	−0.931	[a]	[a]	0.051

[a] H-bond energy could not be calculated due to multiple interactions in addition to the intramolecular hydrogen bond.

employed two methods to estimate this important property, namely isodesmic reactions (as shown in Fig. 1) and the difference in energy between *ortho*- and *para*-isomers. A comparison of the energies gained by the two methods allows an appraisal of the accuracy attained. The value of the electron density at the intramolecular H-bond, ρ, where present, was also calculated as a possible measure of strength.

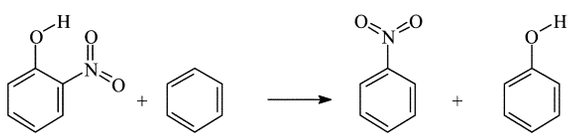


Fig. 1 Isodesmic reaction scheme – example of 2-nitrophenol.

Four properties of complexes of acids with NCH as a reference base were used to predict A, namely the length, denoted r(N ··· H), and stabilisation energy of the H-bond, ΔE, the electron density at the H-bond critical point, ρ(N ··· H), and the transfer of electron density from base to acid, q_{NCH}, as calculated using the NBO scheme.[18] In all cases, formation of a complex with NCH did not substantially change the geometry of the intramolecularly H-bonded acid. As before, basis set superposition error (BSSE) was not included in the calculation of ΔE since inclusion of this term in previous studies was found to give no improvement in the quality of fit.[12] As the values are used in a linear model, the prime concern is the error consistency within the basis set and not the exactitude of the values themselves. All critical point properties were calculated using the AIMPAC program EXTREME.[19] As well as these simple linear relations, we have also applied a recently developed model[13] that uses the molecular electrostatic potential on the van der Waals surface. This is calculated from 6 Å sided cubes consisting of one million equidistant points of electronic density and electrostatic potential, centred on the nuclei of interest. From these two grids, an in-house C-program extracted the local electrostatic potential maxima ($V_{S,Max}$) on the molecular surface, defined as the 0.001 au contour of the electronic density.[20]

Results and discussion

Table 1 reports values of ΔA for 11 *ortho*-substituted phenols, along with the two measures of the strength of the intramolecular H-bond and the value of ρ at the H-bond CP electron density. It is encouraging to note that the two measures of H-bond strength agree well, with a high correlation when plotted against one another ($R^2 = 0.89$). Some small disparities are seen for the weaker H-bonds, with isodesmic reactions generally giving smaller energies. However, the overall similarity gives us confidence that these are accurate estimates of H-bond strengths.

One might anticipate a relation between H-bond strength and the reduction in donor capacity, ΔA, but examination of Table 1 clearly shows that no such relation exists. Plotting ΔA *vs.* H-bond energy gives poor statistics, with $R^2 = 0.16$ or 0.25 depending on the method used to calculate H-bond energy. For instance, 2-hydroxyacetophenone has a very strong H-bond, but its donor ability is only reduced slightly more than 2-chlorophenol, which has a very much weaker H-bond. Korth *et al.*[21] noted the lack of a discernable relationship between H-bond energy and molecular properties for a set of diverse *ortho*-substituted phenols. They could not determine any straightforward correlation between hydrogen bond energy and parameters corresponding to geometrical and spectroscopic changes known to be due to the presence of an intramolecular hydrogen bond, such as the lengths of the O–H bond and H-bond and the stretching frequency of O–H. Likewise, in a study on the structural characteristics of intramolecular hydrogen bonded benzene derivatives, Kovács *et al.*[22] remarked that the non-systematic variation of geometric properties precluded the detection of a relationship with computed hydrogen bond energies.

Similarly, there is no correlation between electron density, ρ, and ΔA, nor indeed between ρ and H-bond strength, which is somewhat surprising given that several previous studies have demonstrated excellent linear relations between these properties for a wide range of H-bond types.[12,23] Instead, the molecules considered fall into two broad classes, *i.e.* those in which the H-bond forms either a five- or six-membered cycle. The former have weaker H-bonds and lower ρ at the H-bond CP than the latter,[24] but within each class there is no trend between these properties.

Calculated properties of hydrogen bond acids with a reference base (following Ref. 12, hydrogen cyanide is used) may be anticipated to give a better correlation with A, since this should account for the fact that some of the acidity of the donor H is sequestered in the intramolecular H-bond. Several properties of acid ··· NCH complexes are known to correlate strongly with A (see electronic supplementary information † for details of correlations used). Table 2 reports values calculated using these relationships and compares them to experimental A values. As well as the 11 intramolecularly H-bonded molecules, we have included three extra compounds for reference, namely phenol, 3-nitrophenol, and 4-nitrophenol, to act as checks that conclusions drawn are reasonable.

The first, and least accurate, correlation uses the distance between the donor H and acceptor N nuclei, r(N ··· H), measured in Å, which as expected shows that acids with greater A values have shorter N ··· H distances. For the 14 molecules in Table 2, this equation predicts A with an accuracy of $R^2 = 0.85$ and rms = 0.13, which although larger than the estimated experimental error, estimated at around 0.05, is rather better than the isolated molecule properties in Table 1. As a result of

Table 2 *A* calculated from properties of NCH complexes

Compound	Expt *A*	*r*(N ··· H) (Å)	*A* from *r*(N ··· H)	*ρ*(N ··· H) (au × 10²)	*A* from *ρ*(N ··· H)	*q*NCH (*e* × 10²)	*A* from *q*NCH	Δ*E* (kJ mol⁻¹)	*A* from Δ*E*
Catechol	0.88	2.01	1.11	2.19	1.06	2.21	0.93	23.52	0.87
2-Hydroxyanisole	0.26	2.19	0.40	1.46	0.34	0.84	0.21	9.24	0.15
2-Chlorophenol	0.32	2.13	0.48	1.71	0.44	1.18	0.31	12.50	0.27
Salicylic acid	0.72	1.94	0.72	2.53	0.77	2.88	0.84	23.10	0.67
Salicylaldehyde	0.11	2.65	0.00	0.52	0.00	[a]		0.00	0.00
2-Hydroxyacetophenone	0.13	2.73	0.00	0.47	0.00	0.11	0.00	0.00	0.00
Methyl 2-hydroxybenzoate	0.04	2.65	0.00	0.52	0.00	[a]		0.00	0.00
2-Nitrophenol	0.05	2.41	0.11	0.91	0.12	0.43	0.09	4.91	0.00
2,4-Dinitrophenol	0.09	2.31	0.24	1.15	0.22	0.71	0.17	9.32	0.15
2,5-Dinitrophenol	0.11	2.30	0.25	1.18	0.23	0.73	0.18	8.95	0.14
2,6-Dinitrophenol	0.17	2.33	0.22	1.13	0.21	[a]		7.61	0.09
Phenol	0.60	2.06	0.57	1.97	0.55	[a]		19.99	0.56
3-Nitrophenol	0.79	1.99	0.66	2.30	0.68	2.52	0.72	27.46	0.84
4-Nitrophenol	0.82	1.99	0.66	2.30	0.68	[a]		27.75	0.85

[a] NBO calculation failed due to linearly dependent basis set.

the correlation equation, if the *r*(N ··· H) exceeds 2.50 Å, the donor hydrogen effectively has no H-bond acidity: two examples where this cut-off is exceeded are 2-hydroxyacetophenone and methyl 2-hydroxybenzoate, which have N ··· H distances of 2.73 Å and 2.65 Å respectively, which are therefore predicted to have $A = 0$. The shortest N ··· H distance found was for 2-chlorophenol (2.13 Å) showing that the acidity of the donor H allows it to form a strong complex with NCH.

Electron density at the hydrogen bond critical point, *ρ*(N ··· H) may also be used to describe H-bond acidity. The anticipated relationship that higher *ρ* indicates better H-bonding and hence a higher *A* value is borne out by the trends observed (observed *vs.* predicted: $R^2 = 0.89$, rms 0.11). Since the *ρ* of the hydrogen bond CP to NCH is found to be very low in 2-hydroxyacetophenone and methyl 2-hydroxybenzoate, these compounds are again calculated to have $A = 0$. Salicylaldehyde and salicylic acid are also seen to display little acidity from the intramolecular hydrogen bonded H.

An additional means of assessing the residual hydrogen bond acidity is the extent of charge transfer from NCH to the acid, $q\mathrm{NCH}_{\mathrm{NBO}}$. The total value for $q\mathrm{NCH}_{\mathrm{NBO}}$ is greater for compounds that show greater hydrogen bond ability, showing charge transfer to the acid from the electron-donating base. Unfortunately, GAUSSIAN98 was unable to compute this property for all complexes due to problems with linearly correlated basis sets. The accuracy of prediction obtained using the remaining nine compounds gave R^2 of 0.95 and rms = 0.08. However, the lack of data for five compounds makes it difficult to evaluate the accuracy of this method compared to the others considered here.

The most accurate property used to estimate *A* considered here is the stabilisation of the acid ··· NCH complex relative to the isolated acid and base, Δ*E*, otherwise known as the intermolecular H-bond strength. The greater the stabilisation (Δ*E*), the stronger the hydrogen bond to NCH and therefore the higher the acidity of the donor hydrogen. This method predicts *A* values with better accuracy than the other models with $R^2 = 0.97$ and rms = 0.05 (see Fig. 2) which approaches the experimental error. Where other properties overestimate *A* for the dinitrophenols, Δ*E* predicts *A* values closer to those experimentally obtained, although little distinction is made between the isomers. Zero H-bond acidity is predicted for 2-nitrophenol and the four compounds containing a carbonyl *ortho* to the phenolic OH: salicylaldehyde, 2-hydroxyacetophenone, methyl 2-hydroxybenzoate and salicylic acid (whose overall *A* is not zero due to the presence of a carboxylic OH group not involved in an intramolecular hydrogen bond). These compounds do not have stable O–H ··· N complexes, suggesting that they are not able to donate acidity from this position. The accuracy of this relationship is encouraging, but, setting *A* to zero for compounds that are known to display some hydrogen bond donor ability does limit the extent to which this model can be applied to those compounds possessing very small hydrogen bond acidities.

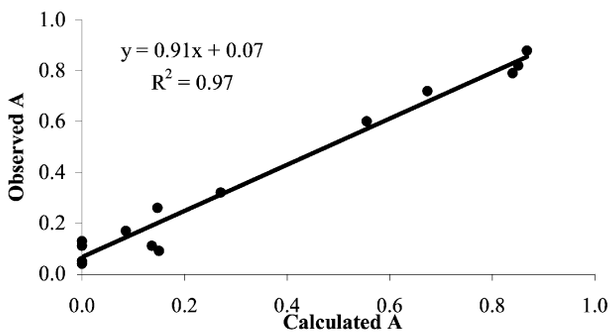


Fig. 2 Observed *vs.* calculated *A* using Δ*E*.

We therefore turned to an alternative method of estimating H-bond acidity, which makes use of the fact that H-bonding contains a significant electrostatic component. Indeed, electrostatic potential has been found to be very useful in modelling H-bond acidity: in a study on the 1 : 1 complexation acidity scale a_2^{H}, Politzer *et al.* demonstrated that a reference base will be attracted to the positive potential regions on the molecular surface.[25] Lamarche *et al.* recently generalised this model to the overall *A* (or Σa_2^{H}) scale,[13] including contributions from secondary H-bond donor sites and removing family dependence by including the local kinetic energy density at the H-bond CP. Using partial least squares methods, the following model of *A* was constructed using 62 diverse, multi-functional acids:

$$A = -0.41 + 7.49\,V_{\mathrm{S,Max}} + 1.24\,V^{1}_{\mathrm{S,Max}} + 5.10\,\Sigma V_{\mathrm{S,Max}} + 25.55\,G \quad (1)$$

where $V_{\mathrm{S,Max}}$ is the global maximum electrostatic potential on the 0.001 au isodensity surface, $V^{1}_{\mathrm{S,Max}}$ the maximum electrostatic potential for any 'stereoisomeric' hydrogens, *e.g.* on an NH_2 group, $\Sigma V_{\mathrm{S,Max}}$ is the sum of the remaining local electrostatic potential maxima on acidic hydrogens, and *G* is the kinetic energy density calculated at the H-bond CP for the most stable acid ··· NCH complex. None of the compounds in the current dataset contains XH_2 groups, so $V^{1}_{\mathrm{S,Max}}$ was set to zero in all cases.

Equation (1) was duly applied to the 14 compounds in Table 1. As expected, *A* values for compounds with no intramolecular hydrogen bond are predicted well. The main contribution to acidity (*i.e.* $V_{\mathrm{S,Max}}$ and *G*) in salicylic acid and catechol comes from hydrogens that are not involved in an intramolecular

Table 3 *A* calculated equation (1)

Compound	Position of $V_{S,Max}$	$V_{S,Max}$ (au)	G_{CP} (au)	Secondary $V_{S,Max}$ (au)	Calc. *A*	Expt. *A*
Catechol	Phenol H	0.0936	0.0122	0.0563	0.97	0.88
2-Hydroxyanisole	Phenol H	0.0592	0.0109	[a]	0.31	0.22
2-Chlorophenol	Phenol H	0.0648	0.0125	[a]	0.39	0.32
Salicylic acid	Carboxylic acid	0.0888	0.0173	0.0268	0.83	0.72
Salicylaldehyde	H *ortho* to carbonyl	0.0389	0.0035	0.0253	0.09	0.11
2-Hydroxyacetophenone	H *ortho* to carbonyl	0.0387	0.0041	0.0196	0.08	0.13
Methyl 2-hydroxybenzoate	Ester methyl H	0.0332	0.0041	0.0231	0.06	0.04
2-Nitrophenol	Phenol H	0.0450	0.0074	[a]	0.12	0.05
2,4-Dinitrophenol	Phenol H	0.0628	0.0092	[a]	0.30	0.09
2,5-Dinitrophenol	Phenol H	0.0588	0.0094	[a]	0.27	0.11
2,6-Dinitrophenol	Phenol H	0.0557	0.0091	[a]	0.24	0.17
Phenol	Phenol H	0.0835	0.0137	[a]	0.57	0.60
3-Nitrophenol	Phenol H	0.0984	0.0158	[a]	0.73	0.79
4-Nitrophenol	Phenol H	0.1050	0.0159	[a]	0.78	0.82

[a] No Secondary maxima present – set to zero in eqn. (1).

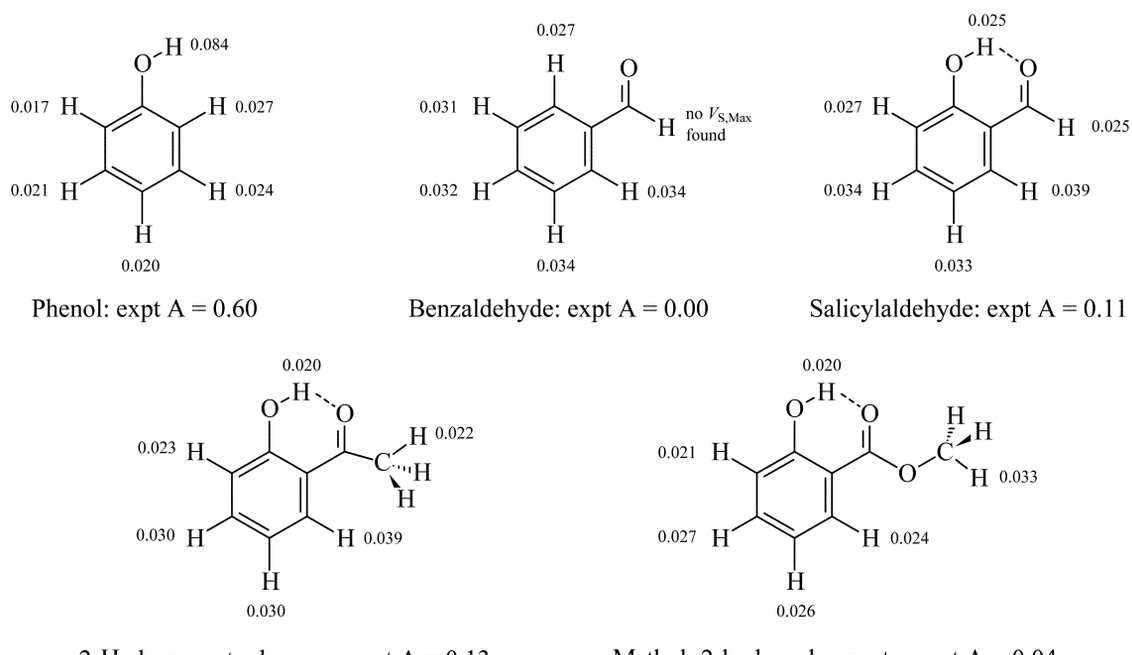


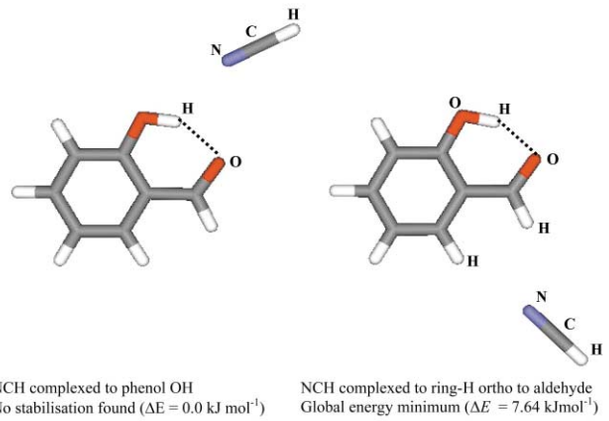
Fig. 3 Local V_S maxima (au) around representative compounds.

hydrogen bond and therefore the internally H-bonded phenolic hydrogen was included only as a secondary contribution (*i.e.* through $\Sigma V_{S,Max}$). In general, excellent overall predictions of *A* were produced using equation 1, as reported in Table 3. For instance, those compounds in which the intramolecular H-bond has only a small effect on the experimental *A* (*e.g.* 2-chlorophenol) are calculated to have relatively high *A* values, while those where *A* is drastically reduced (*e.g.* 2-nitrophenol) have correspondingly low calculated values.

Despite this overall success, some intriguing results came to light during this analysis. Three molecules, salicylaldehyde, 2-hydroxyacetophenone and methyl 2-hydroxybenzoate, are predicted to have physically unrealistic negative *A* values when the phenol-H is taken to be global $V_{S,Max}$. To investigate the source of the small hydrogen bond donor ability in these compounds, electrostatic potential maxima were determined for all hydrogens in salicylaldehyde and its parent compounds: phenol and benzaldehyde (see Fig. 3).

Comparing the O–H in phenol with that in salicylaldehyde shows a three-fold reduction in the maximum electrostatic potential in the latter. This change demonstrates the extent to which intramolecular hydrogen bonding can sequester donor ability. The aromatic C–H's in benzaldehyde and salicylaldehyde are very similar in their $V_{S,Max}$ values, with the exception of the H *ortho* to the carbonyl group. In benzaldehyde, this hydrogen is similar to the others around the ring but in salicylaldehyde, its $V_{S,Max}$ increases such that it becomes the global maximum. Similar analyses of 2-hydroxyacetophenone and methyl 2-hydroxybenzoate (Fig. 3) show that the C–H *ortho* to the carbonyl in the former is the global maximum, with an identical value to salicylaldehyde. Although small, this value is twice that at the phenolic hydrogen, which has a value similar to that of C–H's in benzene. Interestingly, $V_{S,Max}$ in methyl 2-hydroxybenzoate is found at the in-plane ester-methyl hydrogen, inductive effects apparently boosting its H-bond donor ability. However, the maxima for all hydrogens in this compound are low, indicating the overall lack of H-bond acidity (expt. $A = 0.04$).

These results indicate that the effects of intramolecular H-bonding are sufficiently strong to mask the donor ability of the O–H group in these compounds, such that the C–H's come to dominate their *inter*molecular H-bonding. This is further supported by the fact that attempts at geometry optimisation of O–H ⋯ NCH complexes did not result in stable complexes for salicylaldehyde, 2-hydroxyacetophenone and methyl 2-hydroxybenzoate. However, stabilisation does occur if NCH is attached to the global $V_{S,Max}$ site – Fig. 4 shows the most stable salicylaldehyde ⋯ NCH complex found. It is well known that C–H's



NCH complexed to phenol OH
No stabilisation found (ΔE = 0.0 kJ mol^{-1})

NCH complexed to ring-H ortho to aldehyde
Global energy minimum (ΔE = 7.64 kJmol^{-1})

Fig. 4 Two structures of salicylaldehyde ··· NCH complexes investigated.

can be involved in H-bonding, and C–H ··· X H-bonds (where X = O, N, π *etc.*) are frequently seen in such fields as supramolecular chemistry and crystal engineering.[6] That they come to dominate the H-bond donor ability of such polar molecules as salicylaldehyde is remarkable, given the presence of the highly polar O–H group. Further light is shed on this phenomenon by viewing the surface electrostatic potential, shown for salicylaldehyde in Fig. 5. It is immediately apparent that the region of positive electrostatic potential around the O–H, which should attract bases, is almost completely shielded by the surrounding oxygen atoms, and therefore prevented from participating in H-bonding, whereas the C–H's are free to interact.

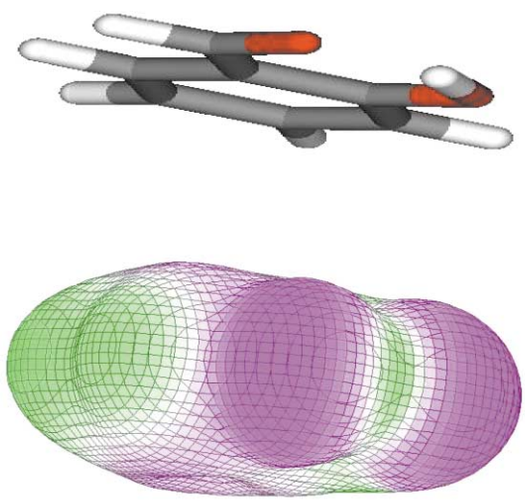


Fig. 5 Orientation and view of electrostatic potential on isodensity surface of salicylaldehyde.

As well as its inherent interest, this fact becomes important when we realise that the $V_{S,Max}$ value in equation (1) should come from the surface of the C–H, while the contribution of O–H should be incorporated into the $\Sigma V_{S,Max}$ term. Treating the molecules noted above in this manner, *i.e.* taking $V_{S,Max}$ and G from the C–H ··· NCH complex and $\Sigma V_{S,Max}$ from O–H, leads to generally excellent predictions of A, as shown in Table 3. Thus, the anomaly that these *ortho*-carbonyl compounds are experimentally found to be weak H-bond donors, but were predicted to have zero or negative acidity is removed, and the source of their acidity identified primarily as C–H bonds.

It is also interesting to compare the three isomers of nitrophenol, which differ not only in the presence of an intramolecular H-bond, but also the extent to which resonance effects play a part. The strong intramolecular H-bond in 2-nitrophenol has been described as "resonance-assisted"[26] and effectively increases the electron-withdrawing ability of the NO_2 group. This in turn increases the acidity of ring hydrogens and the OH group, compared to phenol itself, such that $V_{S,Max}$ is found on the O–H, with a value almost twice that seen at the analogous position in the *ortho*-carbonyl compounds. The H-atoms on the ring possess small $V_{S,Max}$ values of ~0.040 au, and do not contribute to the overall A value. Using the phenolic hydrogen as the sole contributor to A in equation (1) (*i.e.* $\Sigma V_{S,Max}$ set to zero), a reasonable prediction of acidity can be made (expt. $A = 0.05$, calc $A = 0.12$).

These values are very small when compared to 3- and 4-nitrophenol, in which the $V_{S,Max}$ is more than double that in the *ortho*-isomer. The overlap term G is also more than doubled in these isomers, indicating that not only is the electrostatic attraction higher in these isomers, but also that the absence of an intramolecular H-bond allows much greater overlap once a base is attracted to the acidic OH group. The effect of resonance is also apparent in the results reported in Table 3, where it is seen that the difference between 3- and 4-nitrophenol lies exclusively in the electrostatic term $V_{S,Max}$, which is significantly larger in the *para*-isomer than the *meta*. Thus, the electron withdrawing effect of the NO_2 group, expected to be larger for the *para*-isomer, manifests itself by increasing the polarity of the O–H bond, but has little effect on the overlap of electron densities in the H-bond.

The dinitrophenols considered here are also worthy of comment. In general, equation (1) slightly overestimates A values, and properties reported in Table 2 (*e.g.* ΔE) perform rather better in predicting the donor capacity of these molecules. This appears to be a result of overestimating the importance of secondary C–H interactions – the local $V_{S,Max}$ values for these atoms are large (*ca.* 0.05 au), and therefore contribute significantly to acidity through the $\Sigma V_{S,Max}$ in eqn. 1. However, these atoms are not as acidic as their electrostatic potentials may suggest, since repulsions between base and NO_2 groups hinder complex formation. Thus it seems that, in this special case at least, the rather more simplistic approach of considering the stabilisation energy in the global minimum energy complex (forming O–H ··· N H-bonds in this case) performs rather better than the more complex model shown in eqn. 1. Notwithstanding these small difficulties, eqn. 1 performs well overall in predicting experimental A values, with $R^2 = 0.94$ and rms = 0.09. Although the rms is higher than that found using ΔE to predict A, this method has the advantage that acidity is not set to zero for compounds with a small known hydrogen bond donor capacity. Properties of acid ··· NCH complexes cannot be used to predict A from C–H groups since they only take into account properties of complexes and not the initial attractive nature of the molecular electrostatic potential surface. This method allows a detailed analysis of the entire molecule, and hence a fuller appreciation of the effect of intramolecular hydrogen bonding.

Conclusion

Properties of hydrogen bond acids complexed to hydrogen cyanide have been demonstrated to predict hydrogen bond acidity, A, with good accuracy for compounds which contain an intramolecular hydrogen bond. Good correlations were found for several properties: r(N ··· H), the length of the hydrogen bond; ρ(N ··· H), the electron density of the hydrogen bond; qNCH, the extent of charge transfer from NCH to the acid; ΔE, the stabilisation of the complex. Properties of the isolated molecule (hydrogen bond strength and electron density in the H-bond) are poor predictors of A.

The extent to which an intramolecular H-bond causes rearrangement of electron density within a molecule was examined by considering the donor ability of all hydrogens. Electrostatic ($V_{S,Max}$) and overlap (energy density, G) terms accounted for the primary donor site, with local electrostatic maxima accounting for any secondary sites. In most *ortho*-phenol

compounds, the acidity of the OH group is reduced, but this remains the primary donor site. However, in *ortho*-carbonyl phenols it is so severely reduced that the OH effectively has no acidity, such that ring C–H groups become the donor site. As well as analysing a whole compound in considerable detail, this method can also be used to accurately predict *A* values. It is evident that calculation of residual acidity is challenging in compounds containing intramolecular hydrogen bonds since these have multiple and complex effects.

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