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Inductive and resonance effects on the acidities of phenol, enols and carbonyl α-hydrogens.

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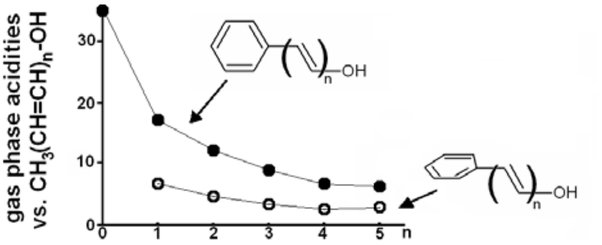
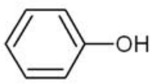


Inductive effects account for 2/5 of the enhanced acidity of phenol and enol, and 1/4 of the enhanced acidity of carbonyl α-hydrogens.

The increased acidity of phenols and carboxylic acids over aliphatic alcohols has traditionally been attributed to resonance stabilization of their (deprotonated) anions[1]. A competing explanation[2] argues that this increase is rather due to destabilization of the acidic proton due to electrostatic effects of the adjacent C=O (in carboxylic acids) or phenyl ring (in phenols). A lively debate on the merits of this proposal has been carried out in the literature[3]. Recent work[4] has shown that in carboxylic acids inductive effects are responsible for 2/3 of the stabilization of the deprotonated anion, but for the case of phenol no solution to the controversy has been forthcoming. Meanwhile, the controversy has entered the undergraduate education textbooks, with some[5] arguing for the traditional view, whereas others[6,7] downplay anion resonance stabilization.

In order to resolve this controversy, we have evaluated resonance, inductive and solvation effects on phenol acidities by performing density-functional calculations on model systems using a methodology first proposed by Holt and Karty[4]. In this methodology, the acidities of the compound of interest (1) and its vinylogues (2) are compared to the acidities of a reference compound (3) and its respective vinylogues (4). The methodology relies on the well-known dependence of the resonance effects on the planarity of the conjugated system: a 90º rotation of the vinylogue chain in (2) removes the resonance contribution of the phenyl substituent, while keeping its σ–bond inductive effect. Therefore, by imposing perpendicularity on the system we may compute the resonance-free acidities of the phenyl vinylogues with increasing length of vinyl groups, and extrapolate the results to the bare phenol. Since the similarity of the solution pKa of phenol (where resonance is hypothesized to be important) to that of enols (where fewer contributing resonance structures are available) has been claimed[7] to disprove the presence of a strong resonance-stabilization effect on phenol, we also performed similar calculations on the enol (6), and its vinylogues (7). Similar calculations on acetaldehyde (8) and its vynilogues (9) were also performed.



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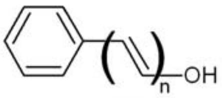

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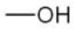

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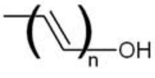

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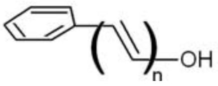

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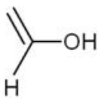

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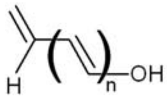

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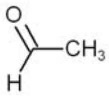

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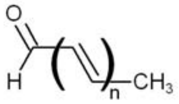

(9)

At the theoretical level used, computed gas-phase acidities (i.e. enthalpies for the reactions AH→ A- + H+) are in very good agreement with experimental values for the analyzed systems (Table 1). We therefore expect that the computed results for the different vinylogues will accurately represent the real values, with an absolute error below the maximmum observed error (4 kcal.mol-1). Differences of acidities between optimized species and species where perpendicularity has been imposed are likely to contain a smaller error, since errors affecting the absolute calculated acidities are expected to cancel when the differences between two similar structures are considered. Analysis of the calculation results allow us to identify the origin of the enhanced acidity of phenol, enol and carbonyl α-hydrogens in acetaldehyde.

Table 1 Comparison of experimental and computed gas-phase acidity enthalpies for relevant reference compounds. All values in kcal.mol-1. Experimental values taken from ref. 8, except for water[9] and methane[10]

	Computed	Experimental
Phenol	347.8	351.4 ± 2.0

Acetaldehyde	366.3	366.4 ± 2.0
Acetone	368.5	368.8 ± 2.0
Isopropanol	375.1	374.1 ± 2.0
Ethanol	377.3	376.1 ± 2.0
Methanol	380.8	379.2 ± 2.0
Water	390.3	390.3
Methane	418.0	418.0 ± 3.5

In the following discussion, vibrational effects have been neglected in order to focus on the electronic effects: unlike the relaxed molecules, the strained conformations of the analyzed vinylogues are not minima in their potential energy landscapes, and therefore inclusion of vibrational effects would add a distracting factor to our study. For the relaxed systems, inclusion of the vibrational effects introduces at most a 1 kcal.mol-1 difference to the acidity enhancements (of phenol and enol relative to methanol and of carbonyl α–hydrogens relative to regular C-H hydrogens) reported.

The gas-phase acidity of phenol (excluding vibrational effects) is 34.8 kcal.mol-1 higher than that of methanol. Incorporation of vinyl units between the aromatic ring and the OH group enhances the acidity of the OH group, as expected from the increase of the resonance effect due to the vinyl chain (Table 2). An acidity increase is also observed as vinyl groups are included between CH3- and OH. However, the difference of acidities between the phenol vinylogues and corresponding vinyl alcohols decreases progressively as the vinyl chain is elongated (Table 3). This decrease might be due either to the progressive weakening of inductive effects of the phenyl ring on the –OH group as the vinyl chain is elongated, or to the fact that the phenyl resonance contributions account for a larger fraction of total resonance when few (or no) vinyl units are present. Inspection of the acidities of the strained conformations of phenol vinylogues (where resonance from the ring is prevented from influencing the OH group) shows that inductive effects consistently account for only 36-38% of the observed acidity enhancement, irrespective of the vinyl chain length. Extrapolation of these values to zero vinyl chain length suggests that inductive effects should not amount to more than 40% of the acidity enhancement observed in the bare phenol.

The gas-phase acidity of enol (6) was found to be 7.2 kcal.mol-1 lower than that of phenol, in contrast to their similar solution pKas. Comparison of gas-phase acidities of vinyl alcohols and enol vinylogues reveals a similar behaviour to that observed previously for the phenol vinylogues: preventing resonance effects through the imposition of perpendicularity on the chemical system strongly reduces the acidifying effect of the H2C=CH- substituent for all vinyl chain lengths studied to less than 40% of that observed in unconstrained systems. Due to the larger delocalization of charge in phenoxide anion vs. acetaldehyde enolate, inclusion of solvation contributions stabilizes the latter much more than the former, and brings their solution acidities to very similar values (298.9 kcal.mol-1 difference between A- and AH for enol vs. 299.2 kcal.mol-1 for phenol), in agreement with the experimentally derived pKas.

Our computations on the acidities of carbonyl α–hydrogens show that the acidity-enhancing effect of the O=CH- group on adjacent C-H decreases from 54.7 kcal.mol-1 to 12.8 kcal.mol-1 (24%) as the geometry is strained to remove resonance effects. As expected, the inductive effect decreases steadily as the methyl group is placed further away from the electron-withdrawing carbonyl.

In summary, this study establishes that inductive effects, while more important than traditionally recognized, do not explain the majority of the observed acidity enhancement in phenol, enols or carbonyl α–hydrogens.

Table 2 Acidities of vinyl alcohols, and phenol, enol , methane and acetaldehyde vinylogues in the gas phase (bold) and in solution. All values in kcal.mol^{-1}. ZPVE not included.

n	CH_3-(CH=CH)$_n$-OH		Ph-(CH=CH)$_n$-OH				H_2C=CH-(CH=CH)$_n$-OH				H-(CH=CH)$_n$-CH_3		O=CH-(CH=CH)n-CH3			
			relaxed		strained		relaxed		strained				relaxed		strained	
0	**389.9**	319.1	**355.1**	299.2			**362.3**	298.9			**427.1**	355.8	**372.4**	310.5	**414.4**	357.0
1	**363.8**	302.6	**347.0**	296.5	**357.3**	301.7	**349.7**	295.2	**358.3**	300.2	**396.4**	337.1	**358.9**	304.5	**384.5**	333.4
2	**351.2**	297.4	**339.3**	293.8	**346.7**	297.3	**342.3**	293.6	**348.8**	296.6	**379.5**	327.1	**351.4**	303.2	**370.2**	324.6
3	**342.9**	294.7	**334.3**	292.7	**339.8**	294.9	**336.9**	292.5	**341.9**	295.4	**368.6**	321.2	**346.1**	302.3	**361.1**	318.9
4	**337.1**	292.8	**330.5**	291.7	**334.7**	293.0	**332.8**	292.0	**336.8**	293.3	**360.8**	317.1	**342.0**	301.9	**354.6**	315.9
5	**332.6**	292.0	**326.7**	290.9	**329.9**	292.3	**329.6**	291.6	**332.8**	292.8	**354.9**	314.5	**338.7**	301.3	**349.5**	313.5

Table 3 Difference of acidities between phenol (or enol) vinylogues and the corresponding vinyl alcohols, and between acetaldehyde vinylogues and corresponding methane vinylogues in the gas phase (bold) and in solution. All values in kcal.mol^{-1}. ZPVE not included.

n	Ph-(CH=CH)$_n$-OH				H_2C=CH-(CH=CH)$_n$-OH				O=CH-(CH=CH)$_n$-CH_3			
	relaxed		strained		relaxed		strained		relaxed		strained	
0	**34.8**	19.9			**27.6**	20.2			**54.7**	45.4	**12.8**	-1.2
1	**16.8**	6.2	**6.5**	0.9	**14.0**	7.4	**5.5**	2.4	**37.5**	32.6	**11.9**	3.7
2	**11.9**	3.6	**4.4**	0.0	**8.9**	3.8	**2.3**	0.8	**28.1**	23.8	**9.3**	2.5
3	**8.6**	2.0	**3.2**	-0.2	**6.0**	2.2	**1.0**	-0.7	**22.6**	18.9	**7.5**	2.3
4	**6.5**	1.1	**2.4**	-0.2	**4.2**	0.8	**0.3**	-0.5	**18.9**	15.3	**6.3**	1.3
5	**6.0**	1.0	**2.7**	-0.4	**3.1**	0.4	**-0.2**	-1.8	**16.2**	13.2	**5.4**	1.0

COMPUTATIONAL DETAILS

All calculations were performed with PcGamess[11], at the Becke3LYP[12] level of theory. Autogenerated delocalized coordinates[13] were used for geometry optimizations, using the 6-31G(d,p) basis set. Zero point (ZPE) and thermal effects (T=298.15 K, P=1 bar) were evaluated using a scaling factor of 0.9804 for the computed frequencies. More accurate energies of the optimized geometries were calculated with the triple-ζ 6-311+G(3d,2p) basis set. Solvation contributions to the stationary points were computed with the polarizable conductor model[14]. Dispersion and repulsion effects were evaluated as described by Amovilli and Mennucci[15].

SUPPORTING INFORMATION AVAILABLE: Atom coordinates and absolute gas phase and solution energies for all molecules studied in this work.

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