

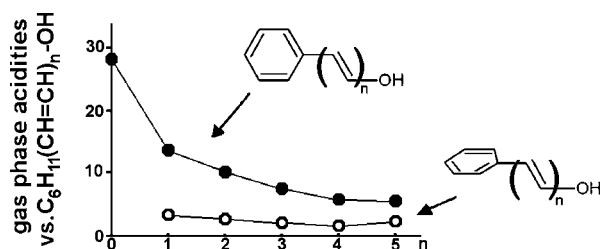
Inductive and Resonance Effects on the Acidities of Phenol, Enols, and Carbonyl α -Hydrogens

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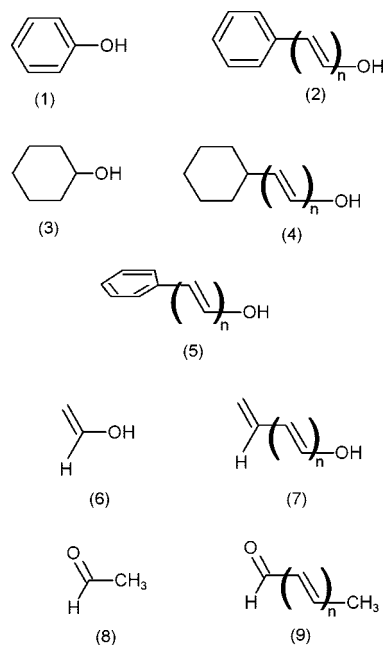


Inductive effects account for 1/3 of the enhanced acidity of phenol versus cyclohexanol, 2/5 of the enhanced acidity of enol versus methanol, and 1/4 of the enhanced acidity of carbonyl α -hydrogens versus methane.

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 explanation² 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 work⁴ 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 regarding the origin of the increased acidity of phenols versus aliphatic alcohols has entered the undergraduate education textbooks, with some⁵ arguing for the traditional view, whereas others^{6,7} downplay anion resonance stabilization.

In order to resolve this controversy, we have attempted to separate “resonance” and “non-resonance” (inductive) 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 suitable 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 90° 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 pK_a of phenol (where resonance is hypothesized to be important) to that of enols (where fewer contributing resonance structures are available, and 35–42% of the total acidity increase has been attributed to inductive effects⁴) has been claimed⁷ 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 vinylogues 9 were also performed.



At the theoretical level used, computed gas-phase acidities (i.e., enthalpies for the reactions $AH \rightarrow A^- + H^+$) 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 maximum 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. Analyses of the calculation results allow us to identify the origin

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TABLE 1. Comparison of Experimental and Computed (at the B3LYP/6-311+G(3d,2p)//6-31G(d,p) Level) Gas-Phase Acidity Enthalpies at 298 K for Relevant Reference Compounds (All Values in kcal·mol⁻¹; Experimental Values Taken from Ref 8 Except for Water⁹ and Methane¹⁰)

	computed	experimental
phenol	347.8	351.4 ± 2.0
acetaldehyde	366.3	365.8 ± 2.2
acetone	368.5	369.1 ± 2.1
isopropanol	375.1	375.4 ± 2.1
ethanol	377.3	377.4 ± 2.1
methanol	380.8	380.6 ± 2.1
water	390.3	390.3
methane	418.0	418.0 ± 3.5

TABLE 2. Acidities of Cyclohexanol (Ch), Phenol, and 2,4-Cyclohexadien-1-ol (2,4Ch) Vinylogues in the Gas Phase at the B3LYP/6-311+G(3d,2p)//6-31G(d,p) Level (All Values in kcal·mol⁻¹; Unlike Table 1, ZPVE and Thermal Effects Have Not Been Included)

<i>n</i>	Ch-(CH=CH) _{<i>n</i>} -OH	Ph-(CH=CH) _{<i>n</i>} -OH		2,4Ch-(CH=CH) _{<i>n</i>} -OH	
		relaxed	strained	relaxed	strained
0	383.2	355.1		379.0	
1	360.6	347.0	357.3	357.5	360.6
2	349.4	339.3	346.7	349.0	348.4
3	341.8	334.3	339.8	341.6	341.2
4	336.3	330.5	334.7	336.3	335.9
5	332.2	326.7	329.9	332.2	331.8

of the enhanced acidity of phenol, enol, and carbonyl α -hydrogens in acetaldehyde.

In the following discussion, vibrational and thermal 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 reported. Different molecules (cyclohexanol and methanol, respectively) were chosen as reference compounds for phenol and enol because the gas-phase acidity of -OH groups has been shown to depend on the polarizability of the attached alkyl group,¹¹ and therefore, phenol and enol acidity increases should be compared with molecules with similar polarizability. A reviewer has also suggested that the presence of π -electrons in phenol may cause anisotropic polarization effects with respect to rotation because of the greater polarizability of π -electrons compared to σ -electrons. This is addressed below.

The enthalpy of deprotonation of phenol (excluding vibrational and thermal effects) is 28.1 kcal·mol⁻¹ lower than that of cyclohexanol. 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 C₆H₁₁ and OH. However, the difference of acidities between the phenol

vinylogues and corresponding cyclohexanol vinylogues 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. The effect of polarization anisotropy of the phenyl substituent was estimated by studying the related 2,4-cyclohexadien-1-ol vinylogues, which contains a small π -system that can be rotated relative to the OH group. It can be seen (Table 2) that the acidities of strained 2,4-cyclohexadien-1-ol vinylogues are very close to that of cyclohexanol vinylogues. It seems therefore natural to attribute the 3.1 kcal·mol⁻¹ difference between the acidities of strained and relaxed strained 2,4-cyclohexadien-1-ol ($n = 1$) vinylogue to factors absent from cyclohexanol vinylogues (e.g., to anisotropy of polarization effects of the π -system). The effect decays very sharply with distance, as evidenced by its absence when more than one vinyl unit is placed between the ring and the OH group. A detailed analysis of the dependence of the difference of the 2,4-cyclohexadien-1-ol ($n = 1$) vinylogue with the dihedral angle between the ring and the OH group was performed (Supporting Information) and compared to a similar analysis performed with the cyclohexanol ($n = 1$) vinylogue. This analysis shows that even in cyclohexanol (where π -polarization effects are absent) a 2 kcal·mol⁻¹ difference in acidity is observed as the ring is rotated relative to the OH group, and therefore not all of the small energy difference observed between strained and relaxed conformations of the 2,4-cyclohexadien-1-ol ($n = 1$) vinylogue is due to anisotropic polarization effects. It seems likely that their effect in phenol acidities will likewise be of minor importance.

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 24–28% of the observed acidity enhancement, irrespective of the vinyl chain length. This observation suggests that at zero vinyl length inductive effects should not amount to more than 1/3 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 (Table 3), in contrast to their similar solution p*K*_a's. Comparison of gas-phase acidities of methanol vinylogues and enol vinylogues reveals a behavior similar 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. Inclusion of solvation contributions brings the solution acidities of phenol and enol 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 p*K*_a's. Two factors may contribute to this observation. On the one hand, due to the larger delocalization of charge in phenoxide anion versus acetaldehyde enolate, inclusion of solvation contributions may stabilize the latter more than the former. On the other hand, as pointed out by a reviewer, a similar behavior is observed in systems where resonance does not play a role: there is a 6 kcal·mol⁻¹ gas-phase acidity difference between ethanol and 3-hexanol, which have similar p*K*_a values in solution. In this instance, the gas-phase acidity

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TABLE 3. Acidities of Methanol, Enol, Methane, and Acetaldehyde Vinylogues in the Gas Phase at the B3LYP/6-311+G(3d,2p)//6-31G(d,p) Level (All Values in kcal·mol⁻¹; Unlike Table 1, ZPVE and Thermal Effects Have Not Been Included)

<i>n</i>	CH ₃ -(CH=CH) _{<i>n</i>} -OH	H ₂ C=CH-(CH=CH) _{<i>n</i>} -OH		H-(CH=CH) _{<i>n</i>} -CH ₃	O=CH-(CH=CH) _{<i>n</i>} -CH ₃	
		relaxed	strained		relaxed	strained
0	389.9	362.3		427.1	372.4	414.4
1	363.8	349.7	358.3	396.4	358.9	384.5
2	351.2	342.3	348.8	379.5	351.4	370.2
3	342.9	336.9	341.9	368.6	346.1	361.1
4	337.1	332.8	336.8	360.8	342.0	354.6
5	332.6	329.6	332.8	354.9	338.7	349.5

TABLE 4. Difference of Acidities between Phenol Vinylogues and the Corresponding Cyclohexanol Vinylogues, Enol Vinylogues, and the Corresponding Methanol Vinylogues, and between Acetaldehyde Vinylogues and Corresponding Methane Vinylogues in the Gas Phase, at the B3LYP/6-311+G(3d,2p)//6-31G(d,p) Level (All Values in kcal·mol⁻¹; ZPVE and Thermal Effects Not Included)

<i>n</i>	Ph-(CH=CH) _{<i>n</i>} -OH		H ₂ C=CH-(CH=CH) _{<i>n</i>} -OH		O=CH-(CH=CH) _{<i>n</i>} -CH ₃	
	relaxed	strained	relaxed	strained	relaxed	strained
0	28.1		27.6		54.7	12.8
1	13.7	3.3	14.0	5.5	37.5	11.9
2	10.2	2.7	8.9	2.3	28.1	9.3
3	7.5	2.1	6.0	1.0	22.6	7.5
4	5.8	1.7	4.2	0.3	18.9	6.3
5	5.5	2.2	3.1	-0.2	16.2	5.4

increase of 3-hexanol versus ethanol has been attributed to the different polarizability of alkyl groups,¹¹ an effect that is masked in solution by the surrounding solvent molecules. The observed similarity of solution pK_a of enol and phenol may therefore also be caused by a similar effect.

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 to 12.8 kcal·mol⁻¹ (24%) as the geometry is strained to remove resonance effects (Table 4). As expected, the inductive effect decreases steadily as the methyl group is placed farther 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. Whether the influence of resonance occurs only on the charge distribution of the deprotonated species or on the potential energy of the acidic proton in the neutral species remains to be ascertained.

Computational Details

All calculations were performed with PcGamess,¹² at the B3LYP¹³ level of theory. Autogenerated delocalized coordinates¹⁴ were used for geometry optimizations, using the 6-31G(d,p) basis set. The *E* configuration was chosen for every C=C bond present

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in the studied vinylogues since this affords more extended conformations, with smaller repulsion effects from the C=C substituents. The twisted structures were optimized subject to the constraint of perpendicularity of the relevant bond. 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.¹⁵ Dispersion and repulsion effects were evaluated as described by Amovilli and Mennucci.¹⁶

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Supporting Information Available: Atom coordinates and absolute gas-phase and solution energies for all molecules studied in this work. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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