

Substituent-controlled phenoxy radical stabilization and HAT thermodynamics in small phenolic antioxidants: an ω B97X-D/CPCM molecular modeling study

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Abstract

Context:

Phenolic antioxidants are widely studied as small-molecule radical scavengers, but their apparent activity depends on the competition among hydrogen-atom transfer (HAT), sequential proton-loss electron transfer (SPLET), and single-electron transfer followed by proton transfer (SET-PT). In this context, the present work uses density functional molecular modeling to clarify how substituent pattern, phenoxy-radical stabilization, and medium effects control site-resolved antioxidant thermodynamics in eleven phenolic compounds, with caffeine and parent coumarin retained as non-phenolic electronic controls.

Methods

Geometry optimizations and harmonic frequency calculations were performed at the ω B97X-D/def2-SVP level, and gas- and solvent-phase single-point energies were refined at ω B97X-D/def2-TZVP using CPCM water, methanol, and benzene. Gibbs free energies were constructed as ESP + Gcorr, while absolute SPLET and SET-PT values used literature H^+ and e^- free-energy constants. HAT was the lowest-energy pathway in all media. Caffeic acid OH1 showed the lowest ΔG_{HAT} values in gas phase, water, methanol, and benzene (66.86, 69.60, 69.54, and 68.29 kcal mol⁻¹, respectively). Spin-density, Mulliken, and NBO/NPA analyses linked favorable HAT to reduced O-centered spin localization and effective π -delocalization in phenoxy radicals. A focused M06-2X benchmark preserved the main ranking, supporting the robustness of the site-selectivity conclusion.

1. Introduction

Phenolic compounds are among the most important molecular classes of natural antioxidants because their O-H groups can quench reactive radical species and form resonance-stabilized phenoxy radicals. The observed antioxidant response in DPPH, ABTS, FRAP, ORAC, and related assays depends on molecular structure, assay medium, pH, reagent stoichiometry, and measurement time; therefore, experimental rankings are often method-dependent rather than universal [1–4]. Computed thermodynamic descriptors are useful because they isolate elementary steps and permit site-specific comparison of related phenolic motifs.

Three mechanisms are commonly invoked for phenolic radical scavenging. In HAT, ArOH transfers a hydrogen atom directly to a radical, and the key descriptor is the O-H bond dissociation free energy or enthalpy. In SPLET, phenol first loses a proton to form ArO⁻ and then transfers an electron. In SET-PT, electron transfer precedes deprotonation of the cation radical. The three mechanisms are not mutually exclusive, and their apparent importance can vary with the medium's polarity and acidity/basicity [5–8].

A robust computational workflow should therefore evaluate the three pathways consistently and avoid overinterpreting a single gas-phase BDE ranking.

Recent computational and experimental work has emphasized the importance of catechol and galloyl motifs, the number and position of hydroxyl groups, and conjugated side chains in stabilizing phenoxy radicals [1, 3, 9]. Caffeic acid, gallic acid, protocatechuic acid, and related hydroxycinnamic or hydroxybenzoic acids frequently appear as strong antioxidant references, whereas mono-hydroxylated or methoxylated analogs are often weaker or more assay-dependent [3, 4, 10]. However, compact datasets that combine absolute ΔG -based HAT/SPLET/SET-PT analysis, atom-resolved spin delocalization, non-phenolic controls, and functional sensitivity remain valuable for method development and natural-product screening.

The present study addresses this gap by constructing a molecular modeling dataset comprising 13 small molecules: 11 phenolic systems and 2 non-phenolic electronic controls. The contribution is fourfold. First, site-resolved HAT, SPLET, and SET-PT pathways are evaluated as Gibbs free energies rather than only electronic or enthalpic components. Second, absolute SPLET and SET-PT totals are obtained by incorporating proton and electron free-energy constants for the gas phase and continuum solvents. Third, spin density, Mulliken, and NBO/NPA descriptors are used to rationalize phenoxy radical stabilization rather than merely to rank O-H bond strengths. Fourth, a focused M06-2X benchmark tests the functional sensitivity of the key site-selectivity conclusions. The work is therefore framed as a substituent- and spin-delocalization analysis of antioxidant thermodynamics, rather than simply another BDE screening exercise.

2. Computational details

2.1. Molecular dataset and controls

The final dataset comprised eleven phenolic compounds and two non-phenolic controls (Table 1). The phenolic set included simple phenols, hydroxybenzoic acids, hydroxycinnamic acids, and methoxylated analogs. Caffeine and parent coumarin were retained as electronic controls to contextualize frontier-orbital and solvation descriptors, but were excluded from phenolic HAT ranking because they lack a phenolic O-H group capable of generating a phenoxy radical under the present mechanistic model.

Table 1
Molecular dataset and mechanistic role of each compound.

Compound	Class	Role	Phenolic O-H sites	Manuscript role
Caffeic acid	hydroxycinnamic acid; catechol motif	Phenolic candidate	2	Strong; lead
Catechol	simple o-diphenol	Phenolic candidate	2	Strong; mechanistic reference
Protocatechuic acid	hydroxybenzoic acid; catechol motif	Phenolic candidate	2	Strong; lead
Gallic acid	trihydroxybenzoic acid	Phenolic candidate	3	Strong; lead
Hydroquinone	p-diphenol	Phenolic candidate	2	Strong; redox-active reference
Syringic acid	dimethoxy-hydroxybenzoic acid	Phenolic candidate	1	Secondary
Ferulic acid	methoxy-hydroxycinnamic acid	Phenolic candidate	1	Secondary
p-Coumaric acid	monohydroxycinnamic acid	Phenolic candidate	1	Secondary
Phenol	simple phenol	Phenolic baseline	1	Baseline
Vanillin	phenolic aldehyde	Phenolic baseline	1	Baseline
Vanillic acid	methoxy-hydroxybenzoic acid	Phenolic baseline	1	Baseline
Coumarin	benzopyrone	Non-phenolic electronic control	0	Excluded from HAT ranking
Caffeine	methylxanthine	Non-phenolic electronic control	0	Excluded from HAT ranking

For visual reference, the optimized geometries of the eleven phenolic compounds are compiled in Scheme 1, whereas the two non-phenolic control molecules are shown separately in Scheme 2. The phenolic set spans simple phenols (phenol, catechol, and hydroquinone), hydroxybenzoic acids (gallic, protocatechuic, vanillic, and syringic acids), and hydroxycinnamic acids (p-coumaric, caffeic, and ferulic acids), thereby covering the principal substitution patterns needed to probe O–H bond strength, radical delocalization, and substituent effects.

The optimized structures highlight the molecular features that control antioxidant thermochemistry. In particular, catechol- and galloyl-type substitution increases the number of candidate O–H donor sites, while conjugated side chains in hydroxycinnamic acids favor spin delocalization after H-atom abstraction. Methoxy substitution modulates both O–H polarity and π -conjugation, allowing direct comparison between hydroxy-only and methoxylated analogs within a common computational framework.

As shown in Scheme 2, coumarin and caffeine provide electronically distinct heteroatom-containing scaffolds that are useful as non-phenolic references. Their inclusion helps distinguish general electronic effects from genuinely phenolic HAT behavior and supports classifying these molecules as electronic controls rather than as primary radical-scavenging candidates in the present dataset.

2.2. Electronic-structure protocol

All calculations used a consistent DFT molecular-modeling protocol for neutral molecules, cation radicals, phenoxy radicals, and phenoxide anions. Geometry optimizations and harmonic frequency calculations were performed with Q-Chem 5.4 at the ω B97X-D/def2-SVP level. Single-point energies were refined at ω B97X-D/def2-TZVP. Solvent effects were modeled by CPCM for water, methanol, and benzene. The range-separated dispersion-corrected ω B97X-D functional was selected as the primary method because it is widely used for thermochemistry and noncovalent/electronic-structure problems [11]. The def2 basis-set family was used for balanced double- and triple-zeta descriptions [12].

Open-shell species were treated as unrestricted doublets. Frequency analyses were used to verify stationary points; only preferred species with zero imaginary frequencies were retained for final thermochemistry. The corrected caffeine cation radical was included only after rescue optimization led to a true minimum. Spin-contamination diagnostics were monitored through $\langle S^2 \rangle$; mild deviations from 0.75 were retained but reported where relevant.

The complete computational protocol and the output used at each stage are summarized in Table 2.

Table 2
Summary of the computational protocol.

Step	Job type	Functional/basis/model	Output used
1	Geometry optimization	ω B97X-D/def2-SVP	Optimized stationary point
2	Frequency	ω B97X-D/def2-SVP	ZPE, thermal corrections, entropy, imaginary frequency check
3	Single point, gas	ω B97X-D/def2-TZVP	Electronic energy for final gas-phase G
4	Single point, solvent	ω B97X-D/def2-TZVP + CPCM	Electronic energy for water, methanol, and benzene
5	Population diagnostics	Mulliken and NBO/NPA single points	Spin/charge descriptors and donor-acceptor trends
6	Benchmark	M06-2X/def2-SVP//def2-TZVP subset	Functional sensitivity for phenol, vanillin, and gallic acid

2.3. Gibbs free-energy definitions

For each species, the final Gibbs free energy was approximated as

$$G \approx E_{\text{SP}}(\omega\text{B97X-D/def2-TZVP}) + G_{\text{corr}}(\omega\text{B97X-D/def2-SVP}).$$

The HAT, SPLET, and SET-PT free energies were computed as follows:

$$\Delta G_{\text{HAT}} = G(\text{ArO}^\bullet) + G(\text{H}^\bullet) - G(\text{ArOH})$$

$$\Delta G_{\text{PA}} = G(\text{ArO}^-) + G(\text{H}^+) - G(\text{ArOH}); \Delta G_{\text{ETE}} = G(\text{ArO}^\bullet) + G(\text{e}^-) - G(\text{ArO}^-)$$

$$\Delta G_{\text{IP}} = G(\text{ArOH}^{+\bullet}) + G(\text{e}^-) - G(\text{ArOH}); \Delta G_{\text{PDE}} = G(\text{ArO}^\bullet) + G(\text{H}^+) - G(\text{ArOH}^{+\bullet})$$

Absolute SPLET and SET-PT totals used literature gas-phase constants and C-PCM solvation Gibbs energies for H^+ and e^- . The electron solvation term is known to be model-dependent, especially in low-polarity media; therefore, absolute SPLET/SET-PT rankings are interpreted qualitatively and primarily in comparison with HAT [13, 14].

2.4. Spin-density, charge, and benchmark analyses

Phenoxy-radical stabilization was quantified from atom-resolved spin densities. For each phenoxy radical, the O-site spin fraction was defined as the O-site positive spin density divided by the sum of positive spin densities over the molecule. The radical delocalization index was defined as $1 - \text{O-site spin fraction}$. A larger index therefore indicates that less spin remains localized on the deprotonated oxygen and more spin is delocalized through the π system.

Mulliken charges were used to define neutral O-H polarity, $q(\text{H}) - q(\text{O})$, and the change in O-site charge upon radical or anion formation. NBO/NPA calculations were also performed for the same output set to inspect natural population/spin trends and donor-acceptor stabilization patterns. A focused M06-2X benchmark was then performed for phenol, vanillin, and the three gallic-acid O-H sites, using the same def2-SVP/def2-TZVP strategy. This benchmark is treated as a functional sensitivity check rather than a full method validation campaign [15, 16]. The overall molecular-modeling workflow used to generate the thermodynamic, spin-density, population-analysis, benchmark, and validation descriptors is summarized in Fig. 1, which should appear immediately below this paragraph.

3. Results and discussion

3.1. Dataset integrity and stationary-point quality

The final master dataset contains 13 molecules, 17 phenolic O-H sites, and 62 preferred species after superseding the original caffeine cation-radical output with a corrected zero-imaginary-frequency structure. All preferred OPT/FREQ species used for thermochemistry displayed zero imaginary frequencies. This stationary-point quality is essential because ΔG values are constructed from frequency-derived corrections. Several open-shell species showed mild spin contamination, but the deviations were not large enough to alter the qualitative ranking or require the exclusion of phenolic candidates. The non-phenolic controls were retained only for electronic comparison, not for HAT ranking.

3.2. HAT is the dominant thermodynamic pathway

Across gas phase, water, methanol, and benzene, the lowest HAT free energies are substantially below the corresponding absolute SPLET and SET-PT totals. Caffeic acid OH1 is the best HAT site in every environment examined, with ΔG_{HAT} values of 66.86 kcal mol⁻¹ in the gas phase, 69.60 kcal mol⁻¹ in water, 69.54 kcal mol⁻¹ in methanol, and 68.29 kcal mol⁻¹ in benzene (Table 3). The next strongest candidates are catechol OH2, gallic acid OH2, hydroquinone OH1/OH2, and protocatechuic acid OH1, depending on the medium. These rankings support a clear structure-activity picture: catechol-like or highly delocalized phenoxy radicals lower the thermodynamic cost of H-atom donation.

The gas-phase site-resolved HAT ranking is visualized in Fig. 2.

Table 3
Top five HAT candidates in each environment.

Medium	Compound	Site	ΔG_{HAT} (kcal mol ⁻¹)
Gas	Caffeic acid	OH1	66.86
Gas	Catechol	OH2	67.88
Gas	Protocatechuic acid	OH1	69.74
Gas	Gallic acid	OH2	70.80
Gas	Hydroquinone	OH1	71.66
Water	Caffeic acid	OH1	69.60
Water	Catechol	OH2	69.96
Water	Gallic acid	OH2	70.36
Water	Hydroquinone	OH2	70.45
Water	Hydroquinone	OH1	70.46
Methanol	Caffeic acid	OH1	69.54
Methanol	Catechol	OH2	69.91
Methanol	Gallic acid	OH2	70.37
Methanol	Hydroquinone	OH2	70.50
Methanol	Hydroquinone	OH1	70.50
Benzene	Caffeic acid	OH1	68.29
Benzene	Catechol	OH2	69.01
Benzene	Gallic acid	OH2	70.63
Benzene	Hydroquinone	OH1	71.26
Benzene	Hydroquinone	OH2	71.27

The lowest mechanism-level free energies and the resulting dominant pathway in each environment are summarized in Table 4.

Table 4
Lowest mechanism free energies across the dataset. Values are in kcal mol⁻¹.

Medium	Lowest ΔG_{HAT}	Lowest absolute ΔG_{SPLET}	Lowest absolute $\Delta G_{\text{SET-PT}}$	Dominant pathway
Gas	66.86	381.42	381.42	HAT
Water	69.60	113.89	113.89	HAT
Methanol	69.54	114.33	114.33	HAT
Benzene	68.29	164.64	164.64	HAT

Although SPLET and SET-PT become much more competitive in polar media than in the gas phase when proton and electron constants are included, their total absolute free energies remain higher than HAT under the selected C-PCM constants. The smallest absolute SPLET/SET-PT totals are 113.89 kcal mol⁻¹ in water and 114.33 kcal mol⁻¹ in methanol, compared with approximately 69.6 kcal mol⁻¹ for the best HAT site. Thus, the dataset supports HAT as the thermodynamic baseline mechanism for these small phenolics. The absolute SPLET and SET-PT totals should nevertheless be discussed with caution, as electron solvation constants are particularly sensitive to the solvation model and reference convention [13].

The comparison of the lowest HAT, SPLET, and SET-PT free-energy totals is shown in Fig. 3.

3.3. Site selectivity in phenolic acids and methoxylated analogs

The site-resolved ranking reveals that not all O-H groups in the same molecule contribute equally. Gallic acid OH2 and OH3 are strongly favored over gallic acid OH1, illustrating the sensitivity of the phenoxy radical to local substitution and resonance pathways. Caffeic acid also shows strong site discrimination: OH1 ranks first overall, whereas OH2 ranks much lower in the gas-phase ranking. The hydroxycinnamic series is especially informative. Caffeic acid outperforms ferulic acid and p-coumaric acid because its catechol motif provides both additional hydrogen-bonding/electronic stabilization and stronger spin delocalization, while ferulic acid and p-coumaric acid remain secondary candidates. The hydroxybenzoic series follows a similar logic: protocatechuic and gallic acids outperform vanillic acid because additional hydroxyl groups enhance radical stabilization, whereas methoxy substitution without an adjacent second phenolic OH gives more moderate behavior.

3.4. Spin delocalization explains phenoxy-radical stabilization

Spin-density analysis provides the electronic-structure explanation for the thermodynamic ranking. The best delocalized phenoxy radicals have lower O-site spin fractions and larger radical delocalization indices. Ferulic acid OH1, caffeic acid OH1, and p-coumaric acid OH1 exhibit the strongest Mulliken

delocalization indices, indicating efficient migration of unpaired spin from the oxygen to the conjugated aromatic/cinnamate framework. Catechol and gallic acid also show strong HAT thermodynamics, but their O-site spin fractions are somewhat higher because spin is distributed among adjacent heteroatom and aromatic centers in a different pattern.

Selected gas-phase Mulliken spin-density and O-H charge descriptors are summarized in Table 5, which should appear immediately below this paragraph. The relationship between gas-phase ΔG_{HAT} and radical delocalization is then illustrated in Fig. 4.

Table 5
Selected gas-phase Mulliken spin-density and O-H charge descriptors.

Site	O-site spin	O-site spin fraction	Delocalization index	q(O) neutral	O-H polarity
Ferulic acid OH1	0.295	0.200	0.800	-0.410	0.752
Caffeic acid OH1	0.285	0.206	0.794	-0.475	0.816
p-Coumaric acid OH1	0.327	0.207	0.793	-0.409	0.740
Vanillin OH1	0.320	0.238	0.762	-0.406	0.750
Syringic acid OH1	0.315	0.239	0.761	-0.400	0.740
Gallic acid OH2	0.328	0.257	0.743	-0.473	0.827
Catechol OH2	0.330	0.276	0.724	-0.485	0.822
Phenol OH1	0.404	0.288	0.712	-0.421	0.747

The NBO/NPA single-point calculations support the same qualitative picture. NPA spin-density rankings identify ferulic acid OH1, p-coumaric acid OH1, and caffeic acid OH1 as highly delocalized radicals, with radical delocalization indices near 0.80. In the manuscript interpretation, these descriptors should be used comparatively within the same computational protocol rather than as direct observables. The charge descriptors further indicate that stronger O-H polarity does not by itself guarantee the lowest HAT free energy; instead, the final ranking emerges from the combined effects of O-H polarity, radical stabilization, and conjugation.

Selected NPA spin-delocalization descriptors for representative phenoxy radicals are summarized in Table 6.

Table 6
Selected NPA spin-delocalization descriptors for phenoxy radicals.

Site	NPA O spin	NPA O-site fraction	NPA delocalization index
Ferulic acid OH1	0.299	0.197	0.803
p-Coumaric acid OH1	0.331	0.203	0.797
Caffeic acid OH1	0.288	0.203	0.797
Vanillin OH1	0.324	0.234	0.766
Syringic acid OH1	0.319	0.235	0.765
Vanillic acid OH1	0.334	0.246	0.754
Protocatechuic acid OH1	0.311	0.253	0.747
Gallic acid OH2	0.332	0.254	0.746

3.5. Functional sensitivity: M06-2X benchmark

A focused M06-2X benchmark was performed on phenol, vanillin, and gallic acid. All benchmark structures reached normal termination and zero imaginary frequencies. M06-2X systematically increased ΔG_{HAT} values by approximately $4.08 \text{ kcal mol}^{-1}$ relative to the primary $\omega\text{B97X-D}$ protocol. However, the qualitative conclusion was conserved: gallic acid OH2 remained the best HAT site in gas phase, water, methanol, and benzene, and the rank order of the key gas-phase sites was unchanged. This provides a method-sensitivity check that the main site-selectivity conclusion is not an artifact of one functional.

The M06-2X benchmark values are summarized in Table 7, and their functional sensitivity trend is shown in Fig. 5.

Table 7
M06-2X benchmark against the primary $\omega\text{B97X-D}$ gas-phase HAT ranking. Energies are in kcal mol^{-1} .

Site	$\omega\text{B97X-D}$ gas ΔG_{HAT}	M06-2X gas ΔG_{HAT}	$\Delta\Delta G$	Rank shift
Gallic acid OH2	70.38	74.57	4.19	0
Gallic acid OH3	71.39	75.72	4.33	0
Phenol OH1	76.45	80.57	4.12	0
Vanillin OH1	77.21	81.25	4.04	0
Gallic acid OH1	77.77	81.98	4.21	0

3.6. Qualitative validation against experimental antioxidant trends

The computed ranking should be compared with DPPH, ABTS, FRAP, and ORAC literature trends qualitatively rather than by direct regression. These assays differ in solvent, pH, radical probe, reaction time, and reporting metric; consequently, the same phenolic compound can shift in apparent rank between assays [2, 4]. Nevertheless, the present ΔG_{HAT} ranking agrees with broad experimental structure-activity patterns. Caffeic acid, catechol-type compounds, protocatechuic acid, and gallic acid are computationally strong and widely recognized as strong radical-scavenging phenolics [3, 4, 10]. Ferulic acid and p-coumaric acid are predicted to be secondary HAT candidates, consistent with the lower activity expected after removal or blocking of a catechol hydroxyl group. Vanillin, vanillic acid, and phenol are predicted as weaker/baseline HAT candidates, consistent with fewer radical-stabilizing structural features.

The qualitative comparison between computed HAT ranking and experimental antioxidant trends is summarized in Table 8.

Table 8
Qualitative comparison between computed HAT ranking and experimental antioxidant trends.

Computed gas rank	Compound	Best site	ΔG_{HAT}	Literature trend	Agreement
1	Caffeic acid	OH1	66.86	Strong DPPH/ABTS; hydroxycinnamic lead	Consistent
2	Catechol	OH2	67.88	Strong o-diphenol radical stabilization	Mechanistically plausible
3	Protocatechuic acid	OH1	69.74	Strong hydroxybenzoic acid	Consistent
4	Gallic acid	OH2	70.80	Frequently strong/standard antioxidant	Consistent
9	Ferulic acid	OH1	74.26	Moderate-to-strong; weaker than caffeic acid	Consistent
10	p-Coumaric acid	OH1	75.33	Moderate; lacks catechol OH	Consistent
14	Vanillin	OH1	77.63	Weak-to-moderate phenolic aldehyde	Consistent
15	Vanillic acid	OH1	77.77	Weak-to-moderate; below gallate/catechol motifs	Consistent

Caffeine and parent coumarin require a different interpretation. Caffeine-containing matrices can show antioxidant behavior, and hydroxylated coumarins can be potent antioxidants, but caffeine and parent coumarin do not possess the phenolic O-H motif required for the phenoxy-radical HAT model. Therefore, they are retained only as non-phenolic electronic controls and excluded from HAT, BDFE, and phenoxy-radical ranking. This classification prevents a mechanistic category error and clarifies that the primary conclusions apply to phenolic O-H donors.

3.7. Implications for molecular modeling of antioxidant mechanisms

The workflow emphasizes chemically interpretable descriptors that can be transferred to larger phenolic libraries. The combination of site-resolved ΔGHAT , absolute SPLET/SET-PT estimates, spin-density delocalization, NBO/NPA population analysis, and functional sensitivity provides a more complete mechanistic picture than a single BDE ranking. This strategy can help prioritize candidate phenolics for experimental validation by DPPH, ABTS, FRAP, or ORAC and identify O-H sites that merit higher-level benchmarking, kinetic analysis, or explicit-solvent treatment. The present results describe thermodynamic tendencies rather than reaction kinetics. No transition-state calculations were performed for reactions with explicit radical probes, and the computed ordering should not be interpreted as a direct prediction of rate constants or assay-specific potency. Continuum solvation does not explicitly represent hydrogen bonding, ion pairing, concentration, or pH, while absolute SPLET and SET-PT values remain dependent on the adopted H^+ and e^- conventions. The M06-2X check was limited to a small subset, and population-based spin and charge descriptors are method dependent. Accordingly, kinetic calculations, explicit-solvent treatment, and compound-specific experiments are needed for further validation.

4. Conclusions

This study establishes a site-resolved DFT molecular modeling framework for the mechanistic analysis of small phenolic antioxidants and demonstrates how substituent effects, solvation, and spin delocalization jointly determine the thermodynamics of antioxidant activity. Across the 13-compound dataset and the 17 phenolic O-H sites examined, the $\omega\text{B97X-D/def2-TZVP} // \omega\text{B97X-D/def2-SVP}$ approach consistently identified HAT as the most favorable antioxidant pathway in gas phase, water, methanol, and benzene when all mechanisms were expressed as Gibbs free energies. Caffeic acid OH1 emerged as the strongest overall HAT candidate, while catechol OH2, protocatechuic acid OH1, gallic acid OH2, hydroquinone OH1, and ferulic acid OH1 also showed favorable reactivity, confirming the benefits of catechol/galloyl substitution and conjugated hydroxycinnamic scaffolds. Spin-density, Mulliken, and NBO/NPA analyses further showed that efficient π -delocalization and reduced O-centered spin localization stabilize the phenoxy radicals and rationalize the computed ΔGHAT ranking. A focused M06-2X benchmark preserved the key qualitative ordering among phenol, vanillin, and gallic acid, indicating that the main mechanistic conclusions are not artifacts of a single functional. Finally, caffeine and parent coumarin are best interpreted as non-phenolic electronic controls rather than as HAT-active

phenolic antioxidants, as they lack a phenolic O–H donor site in the present model. Overall, the combined thermodynamic, spin-delocalization, charge, and literature-validation results identify caffeic acid OH1 as the site with the most favorable HAT thermodynamics in the present series and provide a compact, reproducible foundation for larger-scale molecular screening, subject to the kinetic, solvation, and experimental limitations described above.

Declarations

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author Contribution

FAA conceived the study, performed data analysis, and wrote the initial manuscript draft. YIM, YRY, Sr, DA, and ESS contributed to interpretation, manuscript refinement, and critical discussion. All authors reviewed and approved the final manuscript.

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Data availability

The Q-Chem input/output files, analysis workbooks, and derived descriptor tables are available on Mendeley Data at <https://doi.org/10.17632/3bx98n53ws.1>.

References

1. Chen J, Yang J, Ma L, Li J, Shahzad N, Kim CK (2020) Structure-antioxidant activity relationship of methoxy, phenolic hydroxyl, and carboxylic acid groups of phenolic acids. *Sci Rep* 10:2611.

<https://doi.org/10.1038/s41598-020-59451-z>

2. Baliyan S, Mukherjee R, Priyadarshini A, Vibhuti A, Gupta A, Pandey RP, Chang CM (2022) Determination of antioxidants by DPPH radical scavenging activity and quantitative phytochemical analysis of *Ficus religiosa*. *Molecules* 27:1326. <https://doi.org/10.3390/molecules27041326>
3. Moazzen A, Oztinen N, Ak-Sakalli E, Kosar M (2022) Structure-antiradical activity relationships of 25 natural antioxidant phenolic compounds from different classes. *Heliyon* 8:e10467. <https://doi.org/10.1016/j.heliyon.2022.e10467>
4. Platzer M, Kiese S, Herfellner T, Schweiggert-Weisz U, Eisner P (2022) Radical scavenging mechanisms of phenolic compounds: a quantitative structure-property relationship study. *Front Nutr* 9:882458. <https://doi.org/10.3389/fnut.2022.882458>
5. Wright JS, Johnson ER, DiLabio GA (2001) Predicting the activity of phenolic antioxidants: theoretical method, analysis of substituent effects, and application to major families of antioxidants. *J Am Chem Soc* 123:1173–1183. <https://doi.org/10.1021/ja002455u>
6. Litwinienko G, Ingold KU (2007) Solvent effects on the rates and mechanisms of reaction of phenols with free radicals. *Acc Chem Res* 40:222–230. <https://doi.org/10.1021/ar0682029>
7. Leopoldini M, Russo N, Toscano M (2011) The molecular basis of working mechanism of natural polyphenolic antioxidants. *Food Chem* 125:288–306. <https://doi.org/10.1016/j.foodchem.2010.08.012>
8. Chen Y, Xiao H, Zheng J, Liang G (2015) Structure-thermodynamics-antioxidant activity relationships of selected natural phenolic acids and derivatives: an experimental and theoretical evaluation. *PLoS One* 10:e0121276. <https://doi.org/10.1371/journal.pone.0121276>
9. Palafox-Carlos H, Gil-Chavez J, Sotelo-Mundo RR, Namiesnik J, Gorinstein S, Gonzalez-Aguilar GA (2012) Antioxidant interactions between major phenolic compounds found in Ataulfo mango pulp: chlorogenic, gallic, protocatechuic and vanillic acids. *Molecules* 17:12657–12664. <https://doi.org/10.3390/molecules171112657>
10. Gojak-Salimovic S, Alijagic N, Ramic S (2023) Investigation of antioxidant activity of gallic, protocatechuic and vanillic acid using the Briggs-Rauscher reaction as tool. *Bull Chem Technol Bosnia Herzegovina* 60:7–12. <https://doi.org/10.35666/2232-7266.2023.60.02>
11. Chai JD, Head-Gordon M (2008) Long-range corrected hybrid density functionals with damped atom-atom dispersion corrections. *Phys Chem Chem Phys* 10:6615–6620. <https://doi.org/10.1039/B810189B>
12. Weigend F, Ahlrichs R (2005) Balanced basis sets of split valence, triple zeta valence and quadruple zeta valence quality for H to Rn: design and assessment of accuracy. *Phys Chem Chem Phys* 7:3297–3305. <https://doi.org/10.1039/B508541A>
13. Tosovic J, Markovic S, Milenkovic D, Markovic Z (2016) Solvation enthalpies and Gibbs energies of the proton and electron - influence of solvation models. *J Serbian Soc Comput Mech* 10:66–76. <https://doi.org/10.5937/jsscm1602066T>

14. Fifen JJ, Nsangou M, Dhaouadi Z, Motapon O, Jaidane NE (2013) Solvation energies of the proton in methanol. *J Chem Theory Comput* 9:1173–1181. <https://doi.org/10.1021/ct300669v>
15. Spiegel M, Andruniow T, Sroka Z (2021) Statistically supported antioxidant activity DFT benchmark - the effects of Hartree-Fock exchange and basis set selection on accuracy of thermochemical parameters. *Molecules* 26:505. <https://doi.org/10.3390/molecules26030505>
16. Quang DD, Nguyen TT, Hoang TNA, Le TTH, Truong DH, Pham MQ, Pham QL, Nguyen MC, Doan LP (2022) Antioxidant potential of eight phenolic acids using high-performance density functional theory. *Vietnam J Sci Technol* 60:21–32. <https://doi.org/10.15625/2525-2518/16011>
17. Zhao Y, Truhlar DG (2008) The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements. *Theor Chem Acc* 120:215–241. <https://doi.org/10.1007/s00214-007-0310-x>
18. Mulliken RS (1955) Electronic population analysis on LCAO-MO molecular wave functions. I. *J Chem Phys* 23:1833–1840. <https://doi.org/10.1063/1.1740588>
19. Reed AE, Weinstock RB, Weinhold F (1985) Natural population analysis. *J Chem Phys* 83:735–746. <https://doi.org/10.1063/1.449486>
20. Cossi M, Rega N, Scalmani G, Barone V (2003) Energies, structures, and electronic properties of molecules in solution with the C-PCM solvation model. *J Comput Chem* 24:669–681. <https://doi.org/10.1002/jcc.10189>
21. Q-Chem Inc (2021) Q-Chem 5.4. Q-Chem Inc, Pleasanton, CA, USA.
22. Todorov L, Saso L, Kostova I (2023) Antioxidant activity of coumarins and their metal complexes. *Pharmaceuticals* 16:651. <https://doi.org/10.3390/ph16050651>
23. Liang N, Kitts DD (2014) Antioxidant property of coffee components: assessment of methods that define mechanisms of action. *Molecules* 19:19180–19208. <https://doi.org/10.3390/molecules191119180>

Scheme

Scheme 1 and 2 are available in the Supplementary Files section.

Figures

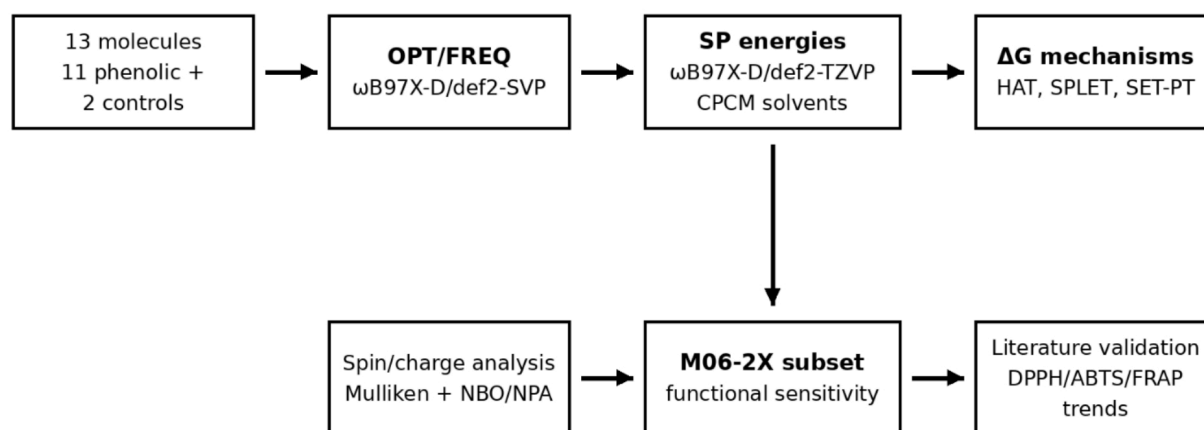


Figure 1

Overview of the molecular-modeling workflow used to convert Q-Chem outputs into mechanistic ΔG values, spin-density descriptors, NBO/NPA population analyses, benchmark data, and literature-validation trends.

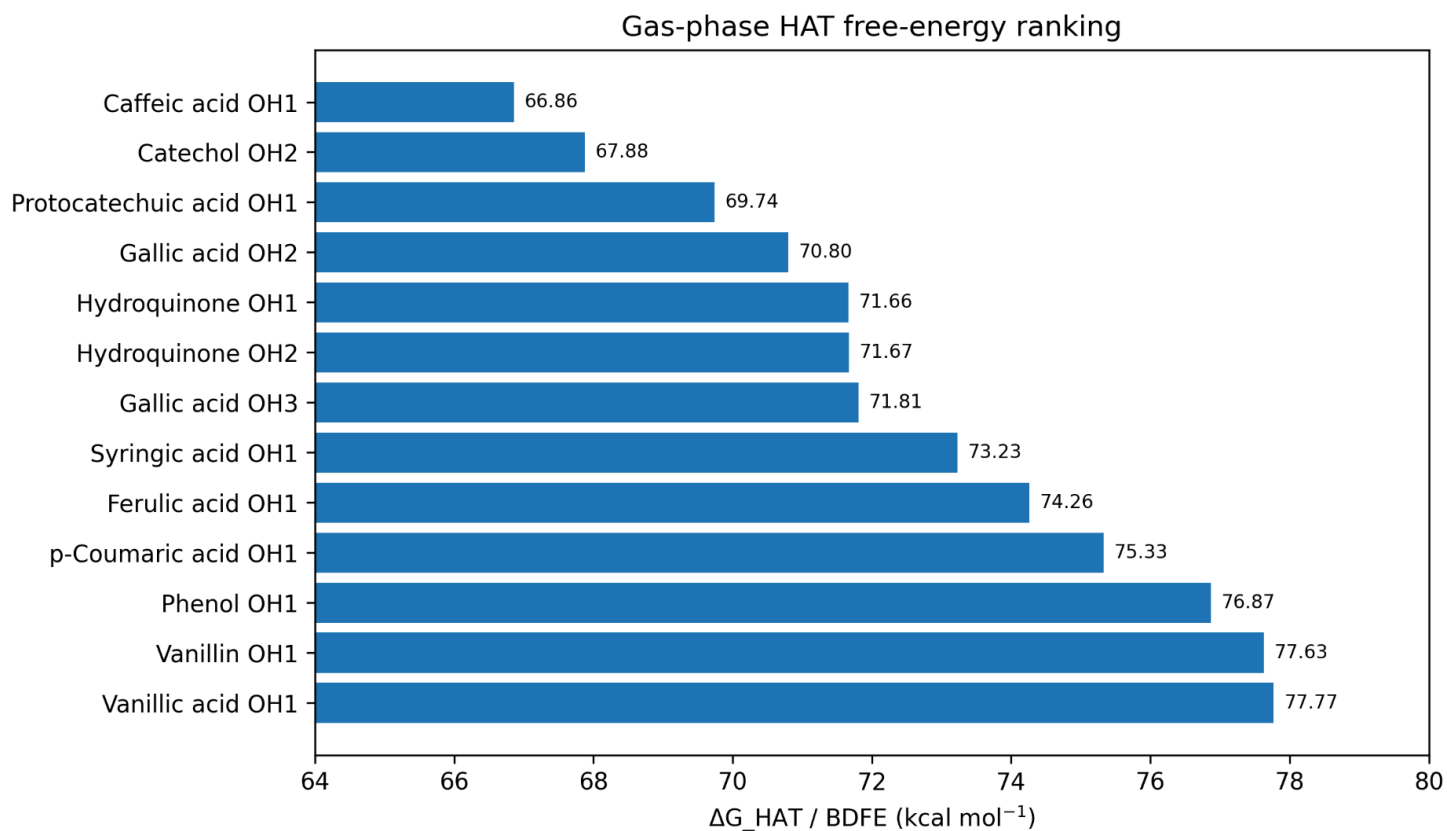


Figure 2

Gas-phase ΔG_{HAT} ranking for selected phenolic O-H sites. Lower values indicate easier H-atom donation and higher predicted HAT efficiency.

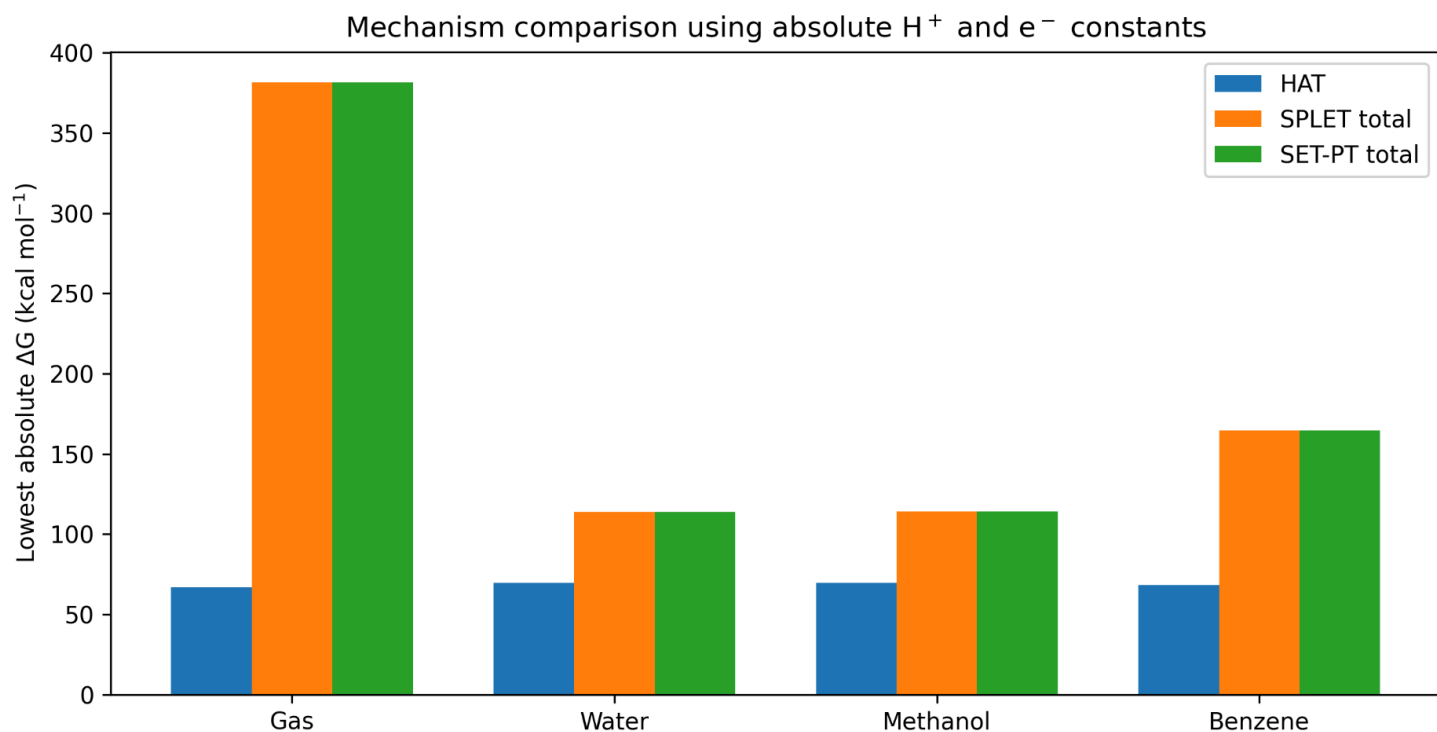


Figure 3

Comparison of the lowest HAT, SPLET, and SET-PT free-energy totals for each environment after including literature H^+ and e^- constants.

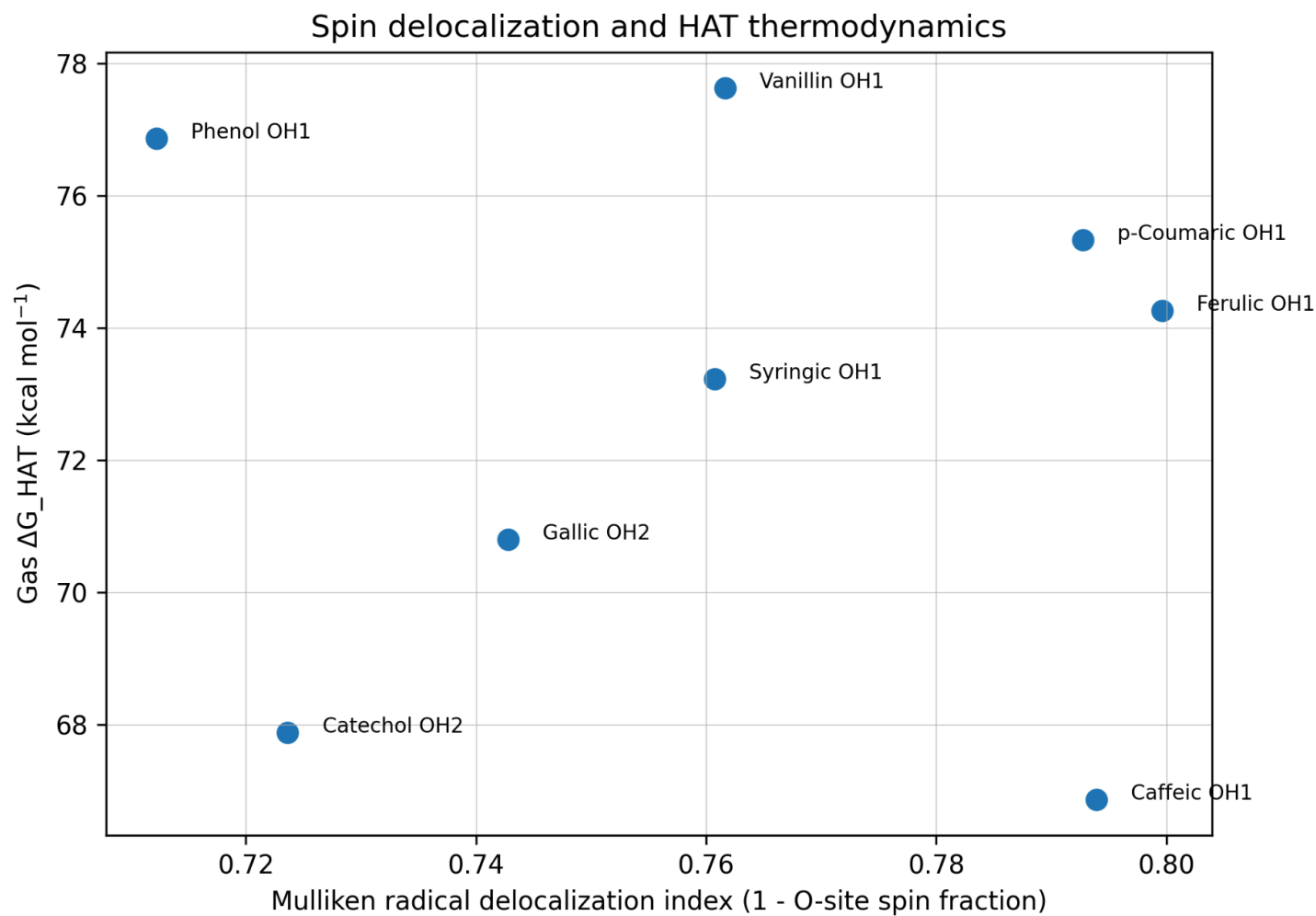


Figure 4

Relationship between gas-phase ΔG_{HAT} and Mulliken radical delocalization index for selected phenoxyl radicals.

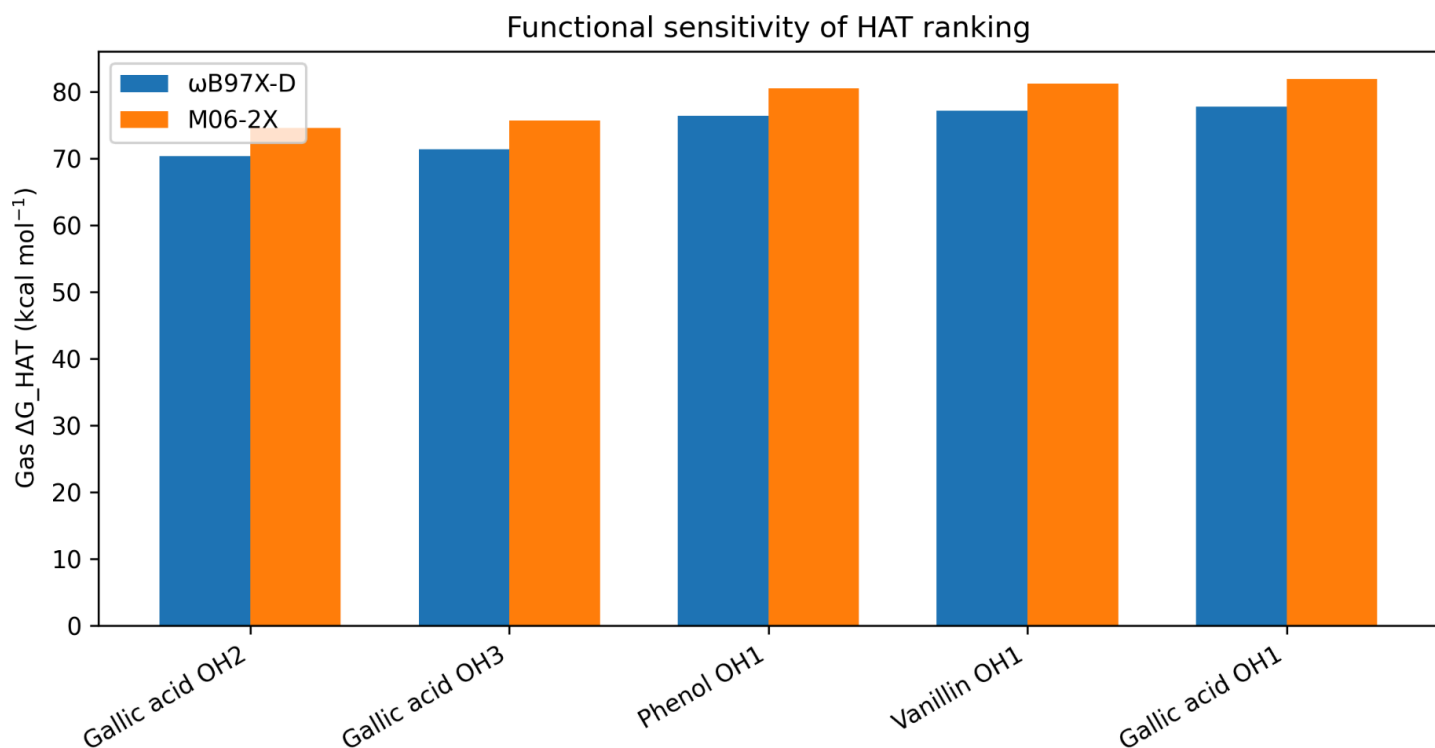


Figure 5

Functional sensitivity of gas-phase HAT free energies for phenol, vanillin, and gallic acid. M06-2X shifts absolute values upward but preserves the key ranking.

Supplementary Files

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- [floatimage1.png](#)
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