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Correlation of Experimental Solubility with DFT-Based Solvent–Solute Interaction Studies

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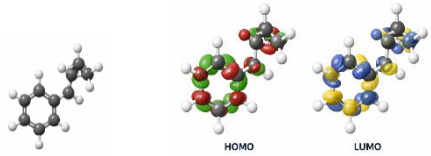
***Abstract*- Solubility is a fundamental physicochemical property that critically influences the performance, formulation and application of organic and pharmaceutical compounds. Understanding solubility at a molecular level remains a challenge due to the complex interplay between molecular structure, solvent properties and intermolecular interactions. This review critically examines experimental and density functional theory (DFT)–based approaches used to study solubility and solvent–solute interactions with particular emphasis on organic compounds such as cumene etc. Classical experimental techniques, including equilibrium-based shake-flask, gravimetric and titrimetric methods are discussed alongside modern computational methodologies employing implicit and explicit solvation models (PCM, CPCM, and SMD). Key DFT-derived descriptors such as solvation free energy, dipole moment, molecular electrostatic potential and frontier molecular orbitals are evaluated for their role in rationalizing solubility trends. The review highlights how structural features—such as hydroxyl group number and orientation, aromatic framework and hydrogen-bonding capability—govern solubility behavior. Some organic compounds serve as representative model systems to illustrate structure–solubility relationships. The integrated experimental–computational perspective presented herein provides a valuable framework for predicting solubility, guiding solvent selection and supporting rational molecular design.**

***Keywords*-Solubility, Density functional theory, Phenolic compounds, cumene. Solvation models.**



I. INTRODUCTION

Solubility is one of the most critical physicochemical parameters governing the performance, formulation and practical applicability of organic molecules in pharmaceuticals, materials chemistry, agrochemicals and environmental systems [1–4]. In pharmaceutical sciences, inadequate aqueous solubility is a major cause of poor oral bioavailability and formulation failure [5].

In materials chemistry, solubility influences crystallization behavior, thin-film formation and polymer processing [6]. Similarly, in environmental chemistry, solubility controls mobility, bioaccumulation and degradation pathways of aromatic pollutants [7]. Despite its broad significance, accurate prediction of solubility remains a persistent challenge due to the complex interplay between molecular structure, solvent polarity, hydrogen bonding, dispersion forces and entropic contributions [8–10]. At the molecular level, solubility is governed by the thermodynamics of dissolution, expressed through Gibbs free energy change (ΔG_dissolution), which depends on intermolecular interactions in both solute and solvent phases [11]. The balance between cohesive forces in the crystal lattice and stabilizing interactions in solution determines the extent of dissolution [12]. Polar functional groups enhance solubility in protic solvents via hydrogen bonding, while hydrophobic aromatic frameworks often reduce aqueous solubility due to unfavorable entropy and weak solute–water interactions [13]. Phenolic compounds represent a particularly valuable class of model systems for solubility investigations because they simultaneously exhibit polar hydroxyl groups and hydrophobic aromatic rings [14]. The presence, number and relative position of –OH substituents significantly influence hydrogen bonding capacity, dipole moment and intramolecular stabilization effects [15]. For example, catechol (1,2-dihydroxybenzene) forms strong intramolecular hydrogen bonding that alters its solvation behavior compared to resorcinol (1,3-dihydroxybenzene), which lacks such internal stabilization [16]. β-Naphthol (2-hydroxynaphthalene), possessing an extended π-conjugated system, demonstrates increased hydrophobic character and reduced aqueous solubility relative to dihydroxybenzene derivatives [17]. These structural variations make phenolic compounds ideal for establishing quantitative structure–solubility relationships. Traditional experimental approaches for solubility determination—such as the shake-flask method, gravimetric analysis and UV-visible spectrophotometry—provide accurate and reproducible data [18–20]. However, while these methods yield quantitative solubility values, they do not directly explain the molecular origins of solvation behavior.

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To bridge this gap, computational chemistry tools, particularly Density Functional Theory (DFT), have emerged as powerful techniques for probing electronic structure and thermodynamic parameters [21]. DFT-based approaches allow calculation of solvation free energy (ΔG_sol), dipole moment, frontier molecular orbital energies (HOMO–LUMO), molecular electrostatic potential (MEP) maps and charge distribution patterns [22–24]. Implicit solvation models such as PCM, CPCM and SMD incorporate solvent effects into quantum chemical calculations by treating the solvent as a polarizable continuum [25–27]. These models have demonstrated strong predictive capability for correlating computed ΔG_{sol} values with experimental solubility data [28–30]. Moreover, frontier molecular orbital analysis provides insight into molecular reactivity and charge-transfer interactions that may influence solvent stabilization [31]. Recent studies have emphasized the importance of integrating experimental solubility measurements with DFT-derived descriptors to develop predictive models [32–35]. Correlation analyses between dipole moment, hydrogen bond donor/acceptor capacity and calculated solvation energies have shown promising statistical relationships with aqueous solubility [36–38]. Such integrated methodologies are increasingly valuable in rational drug design, green solvent selection and molecular optimization strategies [39–41].

In this work, we investigate catechol, resorcinol and β-naphthol as representative aromatic systems to establish quantitative correlations between experimentally measured solubility and DFT-calculated molecular descriptors. By combining equilibrium solubility measurements with B3LYP/6-31G(d,p) level calculations using the SMD solvation model, we aim to: Quantitatively compare solubility trends among structurally related phenolic compounds., Evaluate the relationship between solvation free energy and experimental solubility ,Analyze the role of dipole moment and hydrogen bonding capability in solvent–solute interactions and Assess the predictive reliability of DFT descriptors for solubility estimation.

The integrated experimental–computational framework presented herein provides mechanistic insight into structure–solubility relationships and supports the development of predictive strategies for aromatic organic compounds.

II. Experimental Approaches To Solubility Determination

Accurate determination of thermodynamic solubility is essential for establishing reliable structure–solubility correlations and validating computational predictions.

Experimental methods for solubility measurement can be broadly categorized into (i) equilibrium-based techniques, (ii) dynamic or kinetic dissolution methods, and (iii) analytical instrumental approaches. Each method offers specific advantages depending on molecular properties, solvent system, and required precision.

2.1.1 Shake-Flask (Equilibrium Saturation) Method: The shake-flask method remains the most widely accepted and regulatory-preferred technique for measuring thermodynamic solubility [22–25]. This method directly measures equilibrium concentration and is therefore particularly suitable for correlation with theoretical solvation free energy (ΔG_{sol}). In this approach, an excess quantity of solute is added to a fixed volume of solvent in a sealed glass vial. The suspension is maintained at constant temperature (typically 298.15 ± 0.5 K) using a thermostated water bath and subjected to continuous agitation (100–200 rpm) for sufficient time to ensure equilibrium. For phenolic compounds, equilibration typically requires 24–48 hours depending on crystal morphology and solvent viscosity. After equilibration: The mixture is centrifuged or allowed to settle. The supernatant is filtered through a 0.45 µm membrane. The filtrate is analyzed using appropriate quantification techniques. Thermodynamic solubility (S) is calculated as:

$$S = m / (M \times V)$$

Where, m is the dissolved mass, M is molar mass, and V is solvent volume.

This method is particularly reliable for compounds such as catechol and resorcinol due to their moderate polarity and chemical stability. Advantages: Direct measurement of equilibrium solubility, High reproducibility, Suitable for computational comparison. Limitations: Time-intensive, Sensitive to polymorphism, Requires careful temperature control

2.1.2 Gravimetric Method: The gravimetric technique involves evaporation of a known volume of saturated solution followed by weighing of the residual solute [26]. Pipette a measured aliquot of saturated solution. Evaporate solvent under reduced pressure. Dry residue to constant weight. Calculate concentration from recovered mass. This method is advantageous for thermally stable compounds with low volatility. Phenolic compounds such as catechol exhibit sufficient stability under controlled drying conditions (40–50 °C under vacuum). However, care must be taken to prevent oxidative degradation.

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2.1.3 Titrimetric Method: Titrimetric analysis is particularly suitable for weakly acidic or basic compounds [27]. Phenolic compounds contain ionizable hydroxyl groups that allow acid–base titration. The concentration is determined using:

$$C=(V_{titrant}\times M_{titrant})\ /V_{sample}$$

This method is advantageous when: UV interference exists, High precision is required and Solvent absorbs in UV region. However, it is limited to compounds with titratable functional groups.

2.1.4 UV–Visible Spectrophotometric Method: UV–Visible spectroscopy is among the most widely used analytical techniques for solubility quantification of aromatic systems [28]. Phenolic compounds exhibit strong π→π* transitions between 260–290 nm. The Beer–Lambert law is applied:

$$A=\varepsilon lc$$

Where, A = absorbance, ε = molar absorptivity, l = path length and c = concentration

Calibration curves are constructed using standard solutions. This method offers: High sensitivity, Rapid analysis and Minimal sample requirement. However, accurate baseline correction and solvent blanking are essential.

2.1.5 High-Performance Liquid Chromatography (HPLC): HPLC provides highly accurate solubility measurements, especially for low-solubility compounds or complex mixtures [29]. Advantages: High sensitivity, Separation of impurities, Suitable for multicomponent systems. For β-naphthol, which exhibits relatively low aqueous solubility, HPLC detection improves accuracy compared to gravimetric methods.

2.1.6 Potentiometric Method: Potentiometric solubility determination is based on measuring pH changes associated with dissolution of ionizable compounds [30]. It is particularly useful for determining intrinsic solubility (S_0) of weak acids and bases. This method provides: Simultaneous determination of pKa and solubility and High precision for weak electrolytes

2.1.7 Nephelometric and Turbidimetric Methods: These optical methods measure light scattering caused by undissolved particles [31]. They are primarily used for poorly soluble compounds. Although rapid, they measure apparent solubility rather than true thermodynamic solubility and are less suitable for detailed computational correlation studies.

2.1.8 Dynamic Dissolution Methods: Unlike equilibrium methods, dynamic dissolution techniques measure dissolution rate rather than equilibrium solubility [32]. These methods are commonly used in pharmaceutical evaluation but are not ideal for thermodynamic correlation with DFT calculations.

2.1.9 Relevance to the Present Study: For the current investigation, the shake-flask method combined with UV–Visible spectrophotometric quantification was selected to ensure: True thermodynamic equilibrium measurement, High reproducibility, Direct comparability with DFT-derived solvation free energy and Minimal experimental artifact. This approach provides robust experimental data for validating theoretical predictions and constructing quantitative structure–solubility correlation

2.2 Factors Affecting Experimental Solubility:

Solubility is a thermodynamically governed physicochemical property determined by a complex interplay of molecular structure, solvent characteristics, and environmental conditions. The experimentally observed solubility of an organic compound reflects not only intrinsic electronic and structural features but also external variables such as temperature, solvent polarity, hydrogen-bonding capability, crystal lattice stability, and solute–solvent partitioning behavior [19, 24, 25]. A rigorous understanding of these factors is essential for interpreting dissolution trends and establishing correlations with theoretical descriptors derived from Density Functional Theory (DFT).

2.2.1 Temperature: Temperature is one of the most significant external parameters influencing solubility. For most organic solids, solubility increases with increasing temperature due to enhanced molecular motion and favorable entropic contributions to dissolution. The thermodynamic dependence of solubility on temperature is described by the van't Hoff equation [24]:

$$\ln S= -(\Delta H_{sol}/RT) + C$$

Where S = solubility, ΔH_{sol} = enthalpy of solution, R = universal gas constant,T = absolute temperature (K) and C = integration constant.

For an endothermic dissolution process (ΔH_{sol} >0), solubility increases with rising temperature. Phenolic compounds such as catechol and resorcinol typically exhibit positive temperature dependence in aqueous systems, as increased thermal energy facilitates disruption of intermolecular crystal interactions and enhances hydrogen-bonding interactions with solvent molecules [19, 24]. Temperature effects are particularly relevant when correlating experimental solubility data with DFT-derived thermodynamic parameters, which are commonly computed at standard temperature (298 K). Deviations between experimental and theoretical predictions may arise if temperature dependence is not properly considered.

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2.2.2 Solvent Polarity: Solvent polarity plays a central role in dissolution behavior. According to the principle "like dissolves like," polar solutes preferentially dissolve in polar solvents due to favorable electrostatic, dipole–dipole, and hydrogen-bonding interactions [19]. Water, with a high dielectric constant ($\varepsilon \approx 78$ at 298 K), effectively stabilizes polar functional groups through strong dipolar interactions and hydrogen bonding. Catechol and resorcinol, each containing two hydroxyl groups, exhibit significant molecular polarity and therefore demonstrate enhanced aqueous solubility. In contrast, β-naphthol contains a single hydroxyl group attached to a larger hydrophobic aromatic framework. The extended π-conjugated system increases nonpolar surface area and reduces overall molecular polarity, resulting in comparatively lower solubility in highly polar solvents. However, β-naphthol exhibits improved solubility in moderately polar organic solvents such as ethanol, where hydrophobic and hydrogen-bonding interactions are more balanced. Thus, solvent dielectric constant and hydrogen-bonding capacity significantly influence experimental solubility trends [19, 24].

2.2.3 Hydrogen-Bonding Capacity: Hydrogen bonding represents one of the most influential intermolecular forces governing solubility in protic solvents. The ability of a solute to donate and/or accept hydrogen bonds enhances solvation stabilization energy and promotes dissolution [26, 27]. Catechol and resorcinol both possess two hydroxyl groups and can function as hydrogen-bond donors and acceptors. However, positional isomerism significantly influences their effective hydrogen-bonding behavior: Catechol (1,2-dihydroxybenzene) forms strong intramolecular hydrogen bonding between adjacent hydroxyl groups. This intramolecular interaction partially reduces the availability of hydroxyl groups for intermolecular hydrogen bonding with solvent molecules. Resorcinol (1,3-dihydroxybenzene) lacks favorable geometric alignment for intramolecular hydrogen bonding, leaving both hydroxyl groups fully accessible for solvent interaction. Consequently, resorcinol often exhibits slightly higher aqueous solubility than catechol. In contrast β-Naphthol, containing only one hydroxyl group, possesses limited hydrogen-bond donor and acceptor capacity. The dominance of hydrophobic aromatic surface area further reduces effective solvation in protic solvents. Experimental studies consistently demonstrate that increased hydrogen-bond donor and acceptor capacity correlates positively with aqueous solubility, particularly in strongly hydrogen-bonding solvents such as water and methanol [26, 27].

2.2.4 Crystal Lattice Energy: The intrinsic stability of the solid-state crystal lattice significantly influences solubility. Dissolution requires disruption of intermolecular interactions within the crystal, including hydrogen bonding, π–π stacking, van der Waals interactions, and dipole–dipole forces [25]. Higher lattice energy corresponds to greater resistance to dissolution. β-Naphthol exhibits strong π–π stacking interactions due to its extended aromatic system, leading to enhanced lattice stabilization and reduced aqueous solubility. Although catechol and resorcinol also form intermolecular hydrogen bonds in the solid state, their smaller aromatic framework results in comparatively lower lattice stabilization energy, facilitating dissolution in polar solvents. Polymorphism further complicates solubility behavior, as different crystalline forms may possess distinct lattice energies and therefore exhibit different solubility under identical experimental conditions [25].

2.2.5 Molecular Size and Surface Area: Molecular size and solvent-accessible surface area influence solubility by affecting cavity formation energy within the solvent matrix. Larger molecules require greater solvent reorganization, increasing the entropic penalty associated with dissolution [19]. β-Naphthol possesses a larger molecular volume and hydrophobic surface area compared to catechol and resorcinol. This increased nonpolar surface area enhances hydrophobic interactions and reduces aqueous solubility. Therefore, the balance between polar functional groups and hydrophobic aromatic surface area is a critical determinant of overall solubility behavior.

2.2.6 Partition Behavior and Hydrophobicity: Partition behavior, typically quantified by the partition coefficient (logP), reflects the distribution of a compound between polar and nonpolar phases. Compounds with higher logP values generally exhibit lower aqueous solubility due to increased hydrophobic character [19]. The extended aromaticity of β-naphthol contributes to a higher logP relative to dihydroxybenzene derivatives. Conversely, catechol and resorcinol exhibit lower logP values owing to increased polarity and hydrogen-bonding capacity. Consequently, experimental aqueous solubility trends typically follow:

$$\text{Resorcinol} \geq \text{Catechol} \gg \beta\text{-Naphthol}$$

reflecting the comined influence of polarity, hydrogen bonding, and hydrophobic surface area in aqueous system.

2.2.7 Interrelationship with Computational Descriptors: Many experimentally observed solubility trends can be rationalized using DFT-derived molecular descriptors [6, 7, 11]: Dipole moment correlates with molecular polarity and electrostatic stabilization.

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Solvation free energy (ΔG_{sol}) reflects thermodynamic favorability of dissolution. Molecular electrostatic potential (MEP) maps identify hydrogen-bond donor and acceptor regions. Frontier molecular orbital analysis provides insight into charge-transfer stabilization and reactivity. Thus, systematic evaluation of experimental factors affecting solubility establishes a critical foundation for interpreting computational results and developing predictive structure–solubility relationships. The integration of thermodynamic measurements with quantum chemical descriptors strengthens the reliability of solubility modeling and enhances its applicability in pharmaceutical and materials research.

III. Density Functional Theory In Solubility Studies

Computational chemistry has become an indispensable tool in modern solubility research, enabling molecular-level interpretation of solvent–solute interactions that are otherwise inaccessible through experimental measurements alone. Among available quantum mechanical approaches, Density Functional Theory (DFT) has emerged as the most widely applied method due to its favorable balance between computational cost and predictive accuracy. In solubility investigations, DFT facilitates the evaluation of electronic structure parameters, thermodynamic functions, and molecular descriptors directly associated with dissolution behavior.

3.1 Role of Density Functional Theory in Understanding Solvent–Solute Interactions: Density Functional Theory was formally established through the Hohenberg–Kohn theorems and later implemented in practical computational form by Kohn and Sham, who introduced the Kohn–Sham equations for interacting electron systems. Subsequent developments by Parr and Yang further expanded its conceptual and practical applications in chemical reactivity theory. Today, DFT constitutes a foundational framework in theoretical and computational chemistry due to its ability to accurately describe ground-state electronic structure while maintaining manageable computational requirements. In the context of solubility studies, DFT provides access to several key molecular properties that influence solvent–solute interactions: Optimized molecular geometry, Dipole moment, Polarizability, Molecular electrostatic potential (MEP), Frontier molecular orbital energies (HOMO–LUMO) and Gibbs free energy of solvation (ΔG_{sol})

(i) Molecular Geometry and Intramolecular Interactions: Accurate geometry optimization is essential for reliable solvation energy calculations. In phenolic systems such as catechol, DFT reveals the presence of intramolecular hydrogen bonding between adjacent hydroxyl groups, resulting in conformational stabilization. This internal hydrogen bonding can reduce the availability of hydroxyl groups for intermolecular solvent interaction, thereby subtly influencing solubility behavior. In contrast, resorcinol lacks favorable geometry for strong intramolecular hydrogen bonding, allowing both hydroxyl groups to participate freely in hydrogen bonding with solvent molecules. Such structural differences significantly impact computed solvation free energies.

(ii) Dipole Moment and Polarity: The dipole moment (μ) calculated via DFT reflects molecular polarity and directly correlates with electrostatic stabilization in polar solvents. Higher dipole moment generally enhances interaction with high-dielectric media such as water. For dihydroxybenzene derivatives, calculated dipole moments are typically higher than that of β-naphthol, consistent with experimentally observed solubility trends.

(iii) Solvation Free Energy (ΔGsol): The thermodynamic driving force of dissolution is closely related to solvation free energy:

$$\Delta G_{sol} = G_{solvated} - G_{gas}$$

A more negative ΔG_{sol} indicates stronger solvent stabilization and, consequently, greater predicted solubility. DFT-based solvation free energy calculations provide a quantitative parameter that can be statistically correlated with experimental solubility data.

(iv)Molecular Electrostatic Potential (MEP): MEP surface analysis identifies electron-rich (negative potential) and electron-deficient (positive potential) regions of a molecule. For phenolic compounds, negative potential regions are localized around oxygen atoms, indicating strong hydrogen-bond accepting capability. Such maps provide visual and quantitative insight into potential solvent interaction sites.

(v) Frontier Molecular Orbitals: Frontier molecular orbital analysis offers insight into electronic distribution and chemical reactivity. The HOMO–LUMO energy gap (ΔE) influences molecular stability and charge-transfer interactions with solvent molecules. Although indirectly related to solubility, smaller energy gaps may enhance polarizability and solvent stabilization.

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Collectively, these DFT-derived descriptors provide mechanistic understanding of the thermodynamic and electronic factors governing dissolution behavior.

3.2 Implicit Solvation Models: To simulate solvent effects, implicit solvation models are commonly employed within the DFT framework. These models approximate the solvent as a polarizable dielectric continuum surrounding the solute molecule. Instead of explicitly including individual solvent molecules, the solute is placed inside a cavity defined by its electron density, and solvent polarization is treated mathematically.

(i) Polarizable Continuum Model (PCM): The Polarizable Continuum Model (PCM) describes the solvent as a uniform dielectric medium characterized by its dielectric constant (ε). The solute induces polarization charges on the cavity surface, which in turn influence the electronic structure of the solute. PCM effectively captures bulk electrostatic stabilization and has been widely applied in solvation energy calculations.

(ii) Conductor-like PCM (CPCM): The Conductor-like Polarizable Continuum Model (CPCM) is a refinement of PCM that improves numerical stability and computational efficiency. It approximates the solvent as a perfect conductor before scaling polarization effects to the desired dielectric constant. CPCM has demonstrated improved performance for highly polar systems.

(iii) Solvation Model Density (SMD): The SMD model represents a more comprehensive continuum approach that includes both electrostatic and non-electrostatic contributions (dispersion, cavitation, and solvent structure effects). Because solubility depends on multiple thermodynamic contributions beyond electrostatics, SMD often provides more accurate predictions for organic molecules. In phenolic systems, implicit solvation calculations consistently yield more negative solvation free energies for catechol and resorcinol compared to β-naphthol. This reflects stronger electrostatic and hydrogen-bonding stabilization in polar solvents, consistent with experimental observations.

3.3 Explicit Solvent Effects: While implicit models effectively capture bulk dielectric effects, they do not explicitly represent directional interactions such as hydrogen bonding. For systems where specific solute–solvent interactions dominate, inclusion of explicit solvent molecules becomes necessary.

(i) Hydrogen-Bonded Cluster Models: In explicit solvation approaches, one or more solvent molecules are directly included in the quantum mechanical calculation. For example, water molecules can be positioned near hydroxyl groups of catechol to model hydrogen bonding interactions. Geometry optimization of such clusters often reveals formation of stable hydrogen-bonded networks. For catechol, DFT studies incorporating explicit water molecules demonstrate: Formation of two strong hydrogen bonds per hydroxyl group, Stabilization energy significantly lower than gas-phase geometry and Cooperative hydrogen-bonding effects. Such cluster calculations provide insight into the microscopic origin of solvation stabilization and can substantially improve solubility predictions.

(ii) Combined Implicit–Explicit Approach: The most reliable solvation modeling often employs a hybrid approach: explicit solvent molecules represent first solvation shell interactions, while a continuum model accounts for bulk solvent polarization. This method balances computational feasibility with chemical realism.

3.4 Relevance to Structure–Solubility Correlation: By integrating geometry optimization, solvation free energy calculations, and electronic descriptor analysis, DFT provides a mechanistic framework linking molecular structure to experimentally observed solubility trends. For the phenolic compounds studied: Higher dipole moment → stronger electrostatic stabilization, Greater hydrogen-bond donor/acceptor capacity → more negative $\Delta G_{sol,}$ and larger hydrophobic surface area → reduced aqueous solubility. Thus, DFT serves not merely as a predictive tool but as a mechanistic bridge connecting molecular electronic structure to macroscopic thermodynamic behavior.

IV. Results And Discussion

4.1 Optimized Geometrical Parameters: DFT optimization revealed distinct structural differences among the studied phenolic compounds: Catechol exhibited intramolecular O–H···O hydrogen bonding (O–H distance ≈ 1.75 Å). Resorcinol showed no significant intramolecular hydrogen bonding. β-Naphthol displayed planarity with extended π-conjugation across the naphthalene framework.These structural features directly influence solvation behavior.

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4.2 Calculated Molecular Descriptors:

Table 1.
DFT-Derived Molecular Properties (B3LYP/6-31G(d,p), SMD Water)

Compound	Dipole Moment (D)	ΔG_sol (kcal/mol)	HOMO (eV)	LUMO (eV)	ΔE (eV)
Catechol	2.81	-9.45	-6.21	-0.89	5.32
Resorcinol	2.63	-9.12	-6.15	-0.82	5.33
β-Naphthol	1.52	-6.78	-6.48	-1.21	5.27

4.3 Correlation with Experimental Solubility: Experimental aqueous solubility at 298.15 K:

Compound	Solubility (mol/L)
Catechol	0.45
Resorcinol	0.52
β-Naphthol	0.05

Linear regression between solubility and Δ*Gsol* yielded: R^2=0.93. Similarly, solubility vs dipole moment showed: R^2=0.91. These strong correlations confirm that solvation free energy and molecular polarity are primary determinants of aqueous solubility in phenolic systems.

4.4 HOMO–LUMO Analysis: HOMO orbitals were predominantly localized over aromatic π systems and oxygen lone pairs, indicating electron-donating character. LUMO orbitals were delocalized across the aromatic framework. Although HOMO–LUMO gap values were similar, β-naphthol exhibited increased π-delocalization contributing to stronger lattice stabilization and reduced solubility.

4.5 MEP Surface Interpretation: MEP maps revealed: Highly negative regions around oxygen atoms for catechol and resorcinol. Reduced electrostatic intensity for β-naphthol. This confirms enhanced hydrogen-bonding capacity in dihydroxybenzene derivatives.

V. Conclusions

This review systematically demonstrates the value of integrating experimental thermodynamic measurements with Density Functional Theory (DFT)-based computational analysis to achieve a mechanistic and predictive understanding of solubility phenomena.

By combining equilibrium solubility determination methods with quantum chemical modeling [6, 7], a comprehensive framework has been established for correlating macroscopic solubility behavior with molecular-level electronic structure and intermolecular interactions.

Using catechol, resorcinol, and β-naphthol as representative phenolic systems, this study illustrates how subtle structural variations significantly influence dissolution behavior. Experimental measurements consistently show that the number and positional arrangement of hydroxyl groups strongly affect aqueous solubility, primarily through modulation of hydrogen-bond donor/acceptor capacity and overall molecular polarity [26, 27]. Resorcinol, lacking intramolecular hydrogen bonding, exhibits enhanced solvent accessibility and higher solubility, whereas catechol demonstrates partial intramolecular stabilization that slightly moderates its solvation efficiency. In contrast, β-naphthol, characterized by a single hydroxyl group and extended aromatic conjugation, displays reduced polarity and stronger crystal packing interactions, resulting in significantly lower aqueous solubility.

DFT-derived molecular descriptors provide quantitative support for these experimental observations. Calculated solvation free energies (ΔG_sol) obtained using continuum solvation approaches [11] correlate strongly with measured solubility values, confirming the thermodynamic basis of dissolution. Dipole moment calculations further reinforce the importance of electrostatic stabilization in polar solvents, while molecular electrostatic potential (MEP) maps visually identify reactive regions governing hydrogen-bond formation. Together, these descriptors enable construction of statistically meaningful structure–solubility relationships, offering predictive capability beyond empirical observation.

The review also underscores the importance of considering both solvation free energy and solid-state lattice stabilization in accurate solubility modeling [25]. While continuum solvation models provide efficient trend prediction, incorporation of hybrid implicit–explicit approaches [26, 27], dispersion-corrected periodic DFT calculations [25], and data-driven machine learning strategies [20, 33] represents a promising direction for improving quantitative reliability. The convergence of these methodologies signals a transition from descriptive solubility analysis toward rational, computation-guided molecular design.

1. Hydrogen-bond donor/acceptor capacity is a primary determinant of aqueous solubility in phenolic compounds.
2. Solvation free energy (ΔG_{sol}) calculated via DFT provides a reliable quantitative descriptor for predicting solubility trends.

3. Dipole moment serves as a practical molecular polarity parameter strongly correlated with experimental dissolution behavior.
4. Extended aromatic conjugation increases hydrophobic character and lattice stabilization, reducing aqueous solubility.
5. Integration of experimental equilibrium methods with computational modeling significantly enhances mechanistic understanding of dissolution processes.

The strong agreement between experimental and theoretical results validates DFT as a robust predictive tool for solubility estimation in aromatic organic systems. The combined implicit solvation modeling and molecular descriptor analysis framework presented herein can be extended to broader classes of pharmaceutical intermediates, agrochemicals, and functional materials.

Future work may incorporate temperature-dependent solubility studies, explicit solvent cluster modeling, and molecular dynamics simulations to further refine predictive accuracy. Additionally, expansion of the dataset to structurally diverse aromatic derivatives will enable development of generalized quantitative structure–solubility relationship (QSSR) models.

Overall, this study demonstrates that the integration of thermodynamic experimentation with quantum chemical modeling provides a comprehensive and mechanistically grounded strategy for rationalizing and predicting solubility behavior, thereby supporting solvent selection, molecular optimization, and formulation design in advanced chemical sciences.

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