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A DFT Investigation of Tautomeric Equilibria in 4-Acetamido- and 4-Amino-2-hydroxyquinolines

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Abstract

The tautomeric equilibrium between 2-hydroxyquinoline and 2-quinolone is a fundamental process influencing the properties and reactivity of this important heterocyclic family. Experimental observations have shown that while the 4-amino-7-methyl-2-hydroxyquinoline/4-amino-7-methyl-2-quinolone system exists as a mixture of tautomers, the 4-acetamido-7-methyl-2-hydroxyquinoline/4-acetamido-7-methyl-2-quinolone system is found exclusively as the hydroxy form. This work employs Density Functional Theory (DFT) calculations to elucidate the origin of this different behavior. First, a benchmark study against experimental ¹³C NMR chemical shifts for a set of 30 quinolines identified the MPW1PW91/6-31G(d,p) level of theory as the most suitable for describing these systems. Subsequent analysis of the tautomeric equilibria in the gas phase and various solvents revealed that both systems are thermodynamically biased towards the quinolone form, with the acetamido-substituted system exhibiting a significantly higher kinetic barrier ($\Delta G^\ddagger$) for the reverse tautomerization from the hydroxy to the quinolone form. The orientation of the acetamido group was found to critically influence the molecular dipole moment and the energy gap between tautomers. Furthermore, exploration of explicit interactions with acetic acid, mimicking the experimental conditions, identified several stable minima where the acid molecule stabilizes the 2-hydroxy tautomer, particularly through a dual hydrogen-bond interaction with both the -OH and the acetamido group. This stabilization, combined with the higher kinetic barrier, provides a rationale for the exclusive observation of the 4-acetamido-2-hydroxyquinoline. The findings underscore the subtle interplay of substituent effects, kinetic control, and specific solvent interactions in determining tautomeric preference.

Keywords: Quinoline, Tautomerism, DFT, MPW1PW91, Reaction Mechanisms, Solvent Effects

1 Introduction

Quinolines are privileged heterocyclic scaffolds extensively found in natural products, pharmaceuticals, and functional materials [1, 2]. The presence of a hydroxyl group at the 2-position introduces a prototropic tautomeric equilibrium between the 2-hydroxyquinoline (enol-like) and the 2-quinolone (keto-like) forms. This equilibrium is of paramount importance as it dictates the compound’s electronic structure, hydrogen-bonding capability, and consequently, its biological activity and physicochemical properties [3, 4].

Previous synthetic studies by Cabrera et al. [5–7] reported a intriguing substituent-dependent behavior. In the synthesis of 4-acetamido-2-hydroxy-7-methylquinoline via cyclization of N-(*m*-tolyl)cyanoacetamide in acetic acid/acetic anhydride, the final product was isolated exclusively as the 2-hydroxy tautomer, with no evidence of the corresponding 4-acetamido-7-methyl-2-quinolone. However, upon acidic hydrolysis of the acetamido group, the resulting 4-amino-2-hydroxy-7-methylquinoline existed in equilibrium with its 2-quinolone tautomer, allowing the detection of both species by ^{13}C NMR. This striking difference raises a fundamental question: what factor prevents the tautomerization in the acetamido-substituted system?

While early computational studies have addressed the relative stability of hydroxyquinoline tautomers [4], a detailed comparative analysis of these specific 4-substituted systems under conditions that mimic the synthetic environment is lacking. In this work, we employ DFT calculations to systematically investigate the tautomeric equilibria for both the 4-acetamido and 4-amino-7-methylquinoline systems. Our approach is threefold: (i) we first benchmark several DFT functionals and basis sets against experimental ^{13}C NMR data to select a reliable computational protocol; (ii) we then compute and compare the potential energy surfaces for both tautomerizations in various solvents, including analysis of activation barriers, atomic charges, and dipole moments; and (iii) we explore explicit interactions with acetic acid to model potential catalytic and stabilizing effects of the reaction medium. Our results provide a cohesive rationale for the experimental observations, highlighting the crucial role of the acetamido group in modulating both the kinetic barrier and the specific stabilization by the solvent.

2 Computational Methods

All calculations were performed with the Gaussian 09 software package [8]. Geometry optimizations [9] and frequency calculations [10] were carried out to characterize all stationary points as minima (no imaginary frequencies) or transition states (one imaginary frequency). The initial benchmark study utilized the B3LYP, PBE0, and MPW1PW91 [11] functionals in combination with the Pople-style 6-31G(d,p) and 6-311++G(d,p) basis sets [12]. Isotropic shielding constants were computed using the GIAO method [13, 14] and correlated with experimental ^{13}C NMR chemical shifts from a set of 30 quinolines.

Based on the benchmark results, all subsequent calculations for the tautomeric equilibria were performed using the MPW1PW91 functional. Both basis sets were employed for geometry optimizations, frequency calculations, and NBO population

analyses [15]. Bulk solvent effects were modeled using the Conductor-like Polarizable Continuum Model (CPCM) [16] for five solvents of varying polarity: *n*-heptane, CHCl₃, MeOH, MeCN, and DMSO.

Transition states were located using the quadratic synchronous transit (QST2) method, followed by QST3 refinements [17]. Each transition state was confirmed to have a single imaginary frequency corresponding to the expected proton transfer. Intrinsic Reaction Coordinate (IRC) calculations were performed in both forward and reverse directions to verify that each transition state correctly connected the designated tautomeric minima. Natural Bond Orbital (NBO) analyses were carried out to obtain atomic charges and Wiberg bond indices [18], providing insight into electronic structure and bond order changes along the reaction coordinate. Explicit interaction models with acetic acid were fully optimized at the MPW1PW91/6-31G(d,p) level of theory with the CPCM solvent model (water).

3 Results and Discussion

The two tautomeric equilibria investigated in this work are shown in Figure 1.

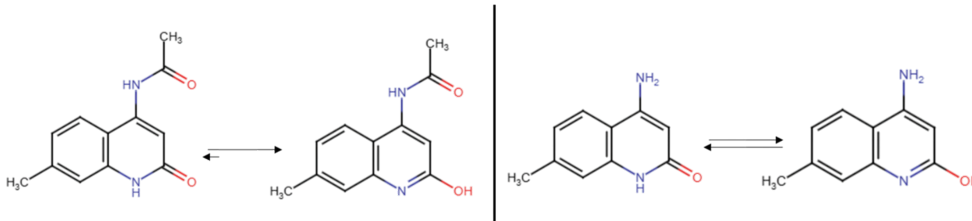


Fig. 1: Tautomeric equilibria studied: (Left) 4-acetamido-2-hydroxy-7-methylquinoline $\rightleftharpoons$ 4-acetamido-7-methyl-2-quinolone; (Right) 4-amino-2-hydroxy-7-methylquinoline $\rightleftharpoons$ 4-amino-7-methyl-2-quinolone.

3.1 Benchmarking the Computational Protocol

To ensure a reliable description of the quinoline systems, we first evaluated the performance of six functional/basis set combinations against experimental ¹³C NMR data for 30 quinolines (molecular groups I-IV in the Supporting Information). Statistical analysis of the correlation between calculated isotropic shielding constants (σ_{calc}) and experimental chemical shifts (δ_{exp}) was performed. After correcting for systematic errors using the regression parameters (m and b from $\delta_{calc} = m \cdot \sigma_{exp} + b$), the MPW1PW91 functional provided the best overall performance. Specifically, the MPW1PW91/6-31G(d,p) combination yielded the highest correlation coefficient ($R^2 = 0.858$) and the lowest corrected root-mean-square error (RMSE_{corr} = 3.03%) when considering only the quinoline ring carbons (C2–C10). The MPW1PW91/6-311++G(d,p) results were very similar ($R^2 = 0.856$, RMSE_{corr} = 3.05%), confirming the robustness of the functional. This benchmark strategy follows previous works

in our group [19] and is consistent with independent assessments of DFT methods for NMR chemical shift prediction [20, 21]. Very recent studies have also validated the MPW1PW91 functional for similar organic systems [22]. Consequently, the MPW1PW91/6-31G(d,p) level was selected for the subsequent exploration of the potential energy surfaces, as it provides an excellent balance between accuracy and computational cost.

3.2 Comparative Analysis of Tautomeric Equilibria

The optimized structures for the tautomers and transition states of both the 4-acetamido and 4-amino systems are shown in Figure 2. A key structural observation is that in the quinolone tautomer (T1), the pyridinone ring exhibits three formal single bonds, disrupting full aromatic conjugation across both rings. In contrast, the 2-hydroxy tautomer (T2) and the transition state (TS) display a fully conjugated, aromatic structure.

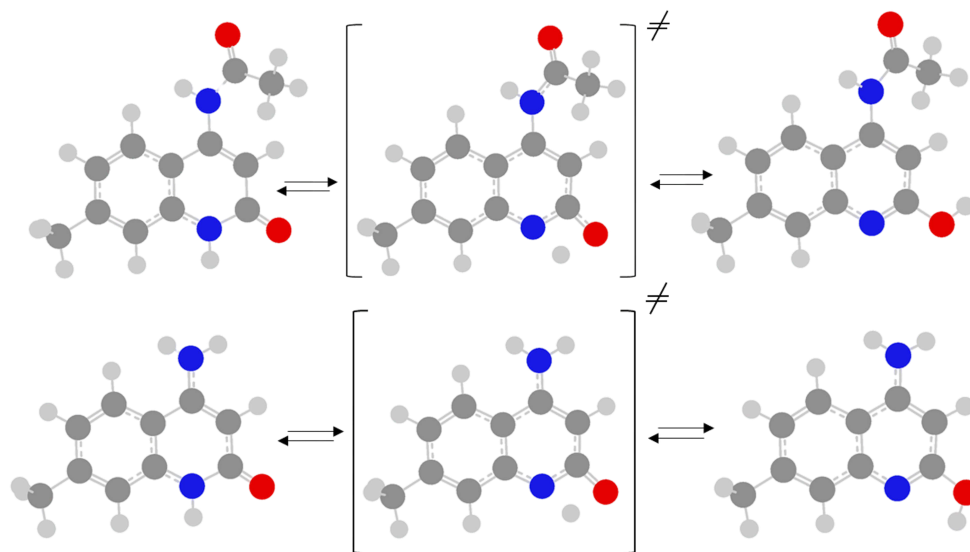


Fig. 2: Optimized structures (MPW1PW91/6-31G(d,p)) of the tautomers and transition states for the 4-acetamido (top) and 4-amino (bottom) systems. Atom color code: C (gray), H (white), N (blue), O (red).

Thermodynamic and kinetic parameters (ΔG_{rxn} and $\Delta G^\ddagger$) for both equilibria in various solvents are summarized in Table 1. Several important conclusions emerge.

Firstly, for both systems in all media, ΔG_{rxn} is positive, indicating that the quinolone tautomer (T1) is thermodynamically more stable than the 2-hydroxy tautomer (T2). This is in agreement with previous theoretical findings for 2-hydroxyquinoline [4] and with the experimental observation for the 4-amino system where both tautomers are detected, but the quinolone is expected to be the major

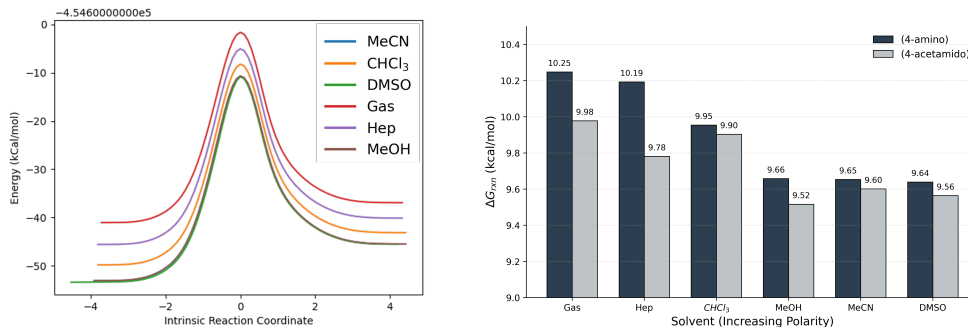
Table 1: Calculated Gibbs free energy differences (ΔG_{rxn}) and activation barriers ($\Delta G^\ddagger$) for the forward (T1 $\rightarrow$ T2) and reverse (T2 $\rightarrow$ T1) reactions at the MPW1PW91/6-31G(d,p) level. All values are in kcal mol⁻¹.

System	Solvent	ΔG_{rxn}	$\Delta G^\ddagger$	
			T1 $\rightarrow$ T2	T2 $\rightarrow$ T1
4-Amino	Gas	+10.25	33.71	23.46
	Heptane	+10.19	34.34	24.14
	CHCl ₃	+9.95	34.91	24.96
	MeOH	+9.66	35.50	25.84
	MeCN	+9.65	35.51	25.86
	DMSO	+9.64	35.55	25.91
4-Acetamido	Gas	+9.98	34.81	24.84
	Heptane	+9.78	36.52	26.74
	CHCl ₃	+9.90	36.53	26.63
	MeOH	+9.52	37.34	27.82
	MeCN	+9.60	37.23	27.63
	DMSO	+9.56	37.24	27.67

component. The thermodynamic preference is very similar for both the amino and acetamido systems, suggesting that the exclusive observation of the hydroxy form in the acetamido case cannot be explained by thermodynamics alone.

Secondly, the kinetic barriers reveal a striking difference. The activation energy for the reverse reaction (T2 $\rightarrow$ T1), i.e., the barrier to convert the 2-hydroxy tautomer back to the quinolone, is consistently higher for the acetamido system than for the amino system. In the acetamido system, $\Delta G_{rev}^\ddagger$ ranges from 24.8 kcal mol⁻¹ (gas) to 27.7 kcal mol⁻¹ (DMSO), whereas in the amino system the range is 23.5–25.9 kcal mol⁻¹. Although the gas-phase values are close, the barrier increases more steeply with solvent polarity for the acetamido system, reaching values that are about 1.8–2.0 kcal mol⁻¹ higher in polar solvents. This implies that once the 4-acetamido-2-hydroxyquinoline is formed, it is kinetically trapped under the reaction conditions, especially in the polar medium used experimentally. The barrier for the forward reaction (T1 $\rightarrow$ T2) is also higher for the acetamido system (34.8–37.2 kcal mol⁻¹) than for the amino system (33.7–35.6 kcal mol⁻¹), indicating that its formation is also slower, but under the experimental conditions (reflux, prolonged time), this barrier can be overcome.

The influence of solvent polarity on the reaction profile is illustrated in Figure 3(a). As the dielectric constant of the medium increases (from gas phase to DMSO), the entire potential energy surface is stabilized, reflected in the more negative relative energies along the IRC coordinate. This behavior is consistent with the charge separation that develops during the proton transfer process. Figure 3(b) shows the ΔG_{rxn} values for both systems. Notably, the 4-acetamido system displays slightly lower ΔG_{rxn} than the 4-amino system across all media, with the difference being more pronounced in gas phase and heptane. This suggests that, although both equilibria



(a) IRC profiles for the 4-acetamido system (b) Reaction free energy (ΔG_{rxn}) for both tautomeric systems (CPCM model).

Fig. 3: (a) Intrinsic Reaction Coordinate (IRC) plots for the 4-acetamido tautomerization in various solvents. The more polar the solvent, the more stabilized the entire potential energy surface becomes, resulting in lower relative energies along the coordinate. (b) Comparison of ΔG_{rxn} for the 4-amino and 4-acetamido systems. The 4-acetamido system exhibits slightly smaller ΔG_{rxn} values, indicating a marginally more favorable thermodynamics for the hydroxy tautomer, especially in non-polar media. The trends for the 4-amino system (not shown for clarity) are analogous to those of the acetamido system; full IRC data for both systems and basis sets are available in the Supporting Information.

favor the quinolone, the hydroxy tautomer is thermodynamically less disfavored in the acetamido case, particularly under non-polar conditions.

3.2.1 Global Hardness Analysis

To further characterize the electronic differences between the two systems, we calculated the global hardness (η), defined as $\eta = (E_{LUMO} - E_{HOMO})/2$. This quantity provides a measure of the resistance to charge transfer and molecular reactivity. The calculated hardness values for both tautomers (T1 and T2) in various solvents are presented in Table 2.

For the 4-amino system, the hardness values of T1 and T2 are very similar across all media, with a slight increase for T2. This indicates a comparable resistance to electronic perturbations for both tautomers, consistent with the observation of an equilibrium. In contrast, for the 4-acetamido system, T2 exhibits a consistently higher hardness than T1, particularly in polar solvents (e.g., DMSO: T1 = 55.936 kcal/mol, T2 = 57.749 kcal/mol). This trend suggests that the 4-acetamido-2-hydroxyquinoline (T2) is electronically less polarizable and more resistant to charge transfer than its quinolone counterpart.

The difference in hardness ($\Delta\eta = \eta_{T2} - \eta_{T1}$) is plotted in Figure 4 as a function of solvent polarity. For the 4-amino system, $\Delta\eta$ decreases markedly from 1.716 kcal mol⁻¹

Table 2: Global hardness (η , in kcal/mol) for the tautomers T1 and T2 of both systems at the MPW1PW91/6-311++G(d,p) level.

System	Tautomer	Solvent				
		Gas	Heptane	CHCl ₃	MeOH	DMSO
4-Amino	T1	56.705	57.320	57.925	58.424	58.456
	T2	58.421	58.565	58.631	58.612	58.606
4-Acetamido	T1	55.582	55.804	55.870	55.946	55.936
	T2	57.141	57.404	57.542	57.749	57.749

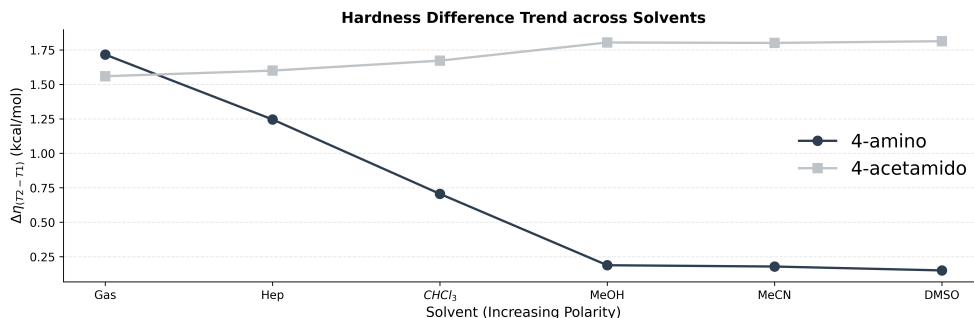


Fig. 4: Difference in global hardness ($\Delta\eta = \eta_{T2} - \eta_{T1}$) as a function of solvent polarity for the 4-amino and 4-acetamido systems. A positive $\Delta\eta$ indicates that the 2-hydroxy tautomer is harder (less reactive) than the quinolone. The 4-acetamido system shows a significantly larger and more solvent-sensitive $\Delta\eta$, especially in polar media, supporting its enhanced kinetic stability.

in the gas phase to 0.188 kcal mol⁻¹ in MeOH, after which it remains nearly constant (0.150 kcal mol⁻¹ in DMSO). In contrast, the 4-acetamido system exhibits a modest increase from 1.559 kcal mol⁻¹ (gas) to 1.803 kcal mol⁻¹ (MeOH), reaching a plateau at 1.813 kcal mol⁻¹ in DMSO. The decreasing slope for the amino system is much steeper than the increasing slope for the acetamido system. This behavior indicates that the electronic difference between the tautomers becomes less pronounced in polar media for the 4-amino system, while for the 4-acetamido system the 2-hydroxy tautomer remains consistently harder (less reactive) than the quinolone, especially in polar solvents. This electronic rigidity, which is absent in the amino system, likely contributes to the kinetic trapping of the hydroxy form and aligns with the experimental observation that it is the sole product detected.

3.2.2 Influence of the Acetamido Group Orientation

The orientation of the flexible acetamido group was found to be a critical factor influencing the relative stability of the tautomers. The initial structures (denoted M1) featured a specific orientation of the acetamido carbonyl and the 2-OH group. However,

a systematic conformational search revealed a lower-energy conformer (M2), shown in Figure 5, where the carbonyl of the acetamido group is oriented away from the quinoline ring and the O-H bond points toward N1. The impact of this conformational change on the thermodynamic and kinetic parameters is summarized in Table 3.

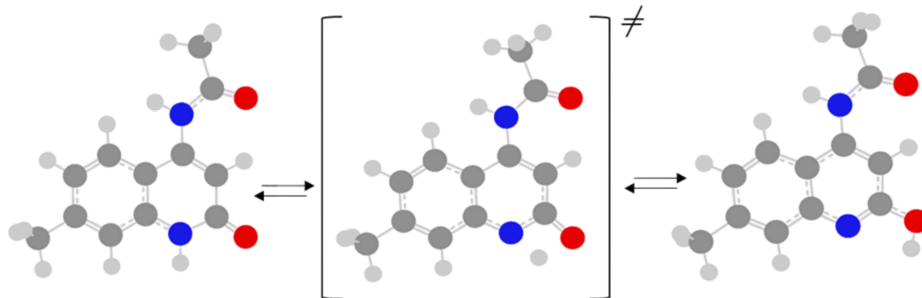


Fig. 5: The lower-energy M2 conformer of the 4-acetamido-2-hydroxyquinoline, showing the O-H bond oriented towards N1 and the acetamido carbonyl pointing away.

Table 3: Comparison of gas-phase thermodynamic parameters (kcal mol^{-1}), activation barriers (kcal mol^{-1}), and dipole moments (Debye) for the M1 and M2 conformers of the 4-acetamido system at the MPW1PW91/6-311++G(d,p) level.

Conformer	ΔG (kcal mol^{-1})			$\Delta G^\ddagger$ (kcal mol^{-1})		$ \bar{\mu}_E $ (Debye)
	T1	T2	TS	T1 $\rightarrow$ T2	T2 $\rightarrow$ T1	
M1	-454201.01	-454190.85	-454164.58	36.43	26.27	T1: 5.32 / T2: 0.56
M2	-454529.98	-454526.01	-454493.89	36.08	32.12	T1: 8.33 / T2: 4.98

The reorientation from M1 to M2 reduces the energy gap between T1 and T2 from 10.16 to 3.96 kcal mol^{-1} , making the two tautomers nearly isoenergetic. More importantly, the activation barrier for the reverse reaction (T2 $\rightarrow$ T1) increases from 26.27 kcal mol^{-1} in M1 to 32.12 kcal mol^{-1} in M2, while the forward barrier remains essentially unchanged (36.43 vs 36.08 kcal mol^{-1}). This indicates that in the more stable M2 conformer, the 2-hydroxy tautomer is not only closer in energy to the quinolone but also kinetically more protected against reversion.

The dipole moment of T2 increases significantly from 0.56 D in M1 to 4.98 D in M2, approaching the values observed for the 4-amino system (where T2 = 3.68 D). This suggests that the conformational preference of the acetamido group may contribute to a better stabilization of the 2-hydroxy tautomer through more favorable solute-solvent interactions in polar media, although explicit solvation effects were not evaluated at this level. The M2 conformer, which is likely the dominant species under the experimental conditions, thus represents a more accurate model for understanding the reactivity of the system.

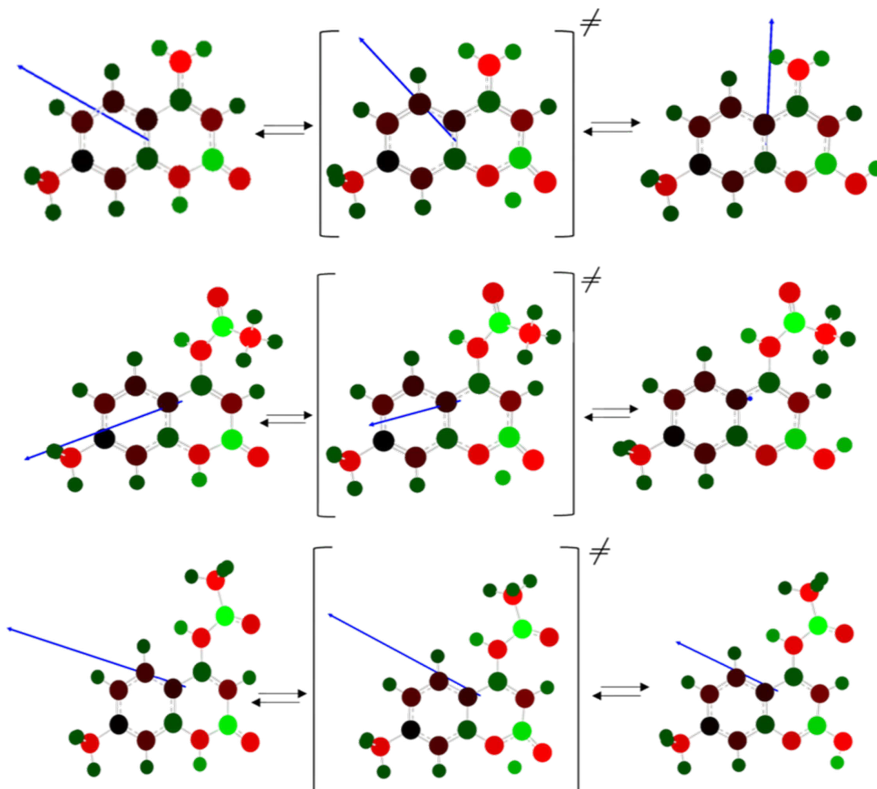


Fig. 6: Partial atomic charges (NBO) for the three systems: (a) 4-amino equilibrium, (b) 4-acetamido M1, (c) 4-acetamido M2. Color scale: red (negative) to green (positive). Color ranges: (a) $[-0.778, 0.778]e$, (b) $[-0.697, 0.697]e$, and (c) $[-0.689, 0.689]e$. Dipole moment vectors are shown as blue arrows.

The electronic distribution across the three systems (4-amino, 4-acetamido M1, and 4-acetamido M2) is visualized in Figure 6, where atoms are colored according to their NBO partial charges. The scale ranges from red (negative charge) to green (positive charge).

In the 4-amino system, both tautomers and the transition state show similar charge distribution patterns, with a gradual change in dipole moment along the reaction coordinate. For the acetamido system, the M1 conformer exhibits a very low dipole moment for T2 (0.56 D), reflecting a nearly symmetric charge distribution. In contrast, the M2 conformer displays a more polarized structure, with a dipole moment of 4.98 D for T2, much closer to that of the amino counterpart. This enhanced polarization likely contributes to the better solvation of T2 in polar media and, together with the increased kinetic barrier, explains why the 4-acetamido-2-hydroxyquinoline is experimentally observed as the sole product.

3.3 Exploring Explicit Solvent Interactions with Acetic Acid

Given that the synthesis was carried out in an acetic acid/acetic anhydride medium, we explored explicit interactions between the 4-acetamido system and acetic acid. An acid-catalyzed mechanism was proposed (Figure 7), involving protonation of the quinolone carbonyl by acetic acid, followed by deprotonation of the N1-H by acetate.

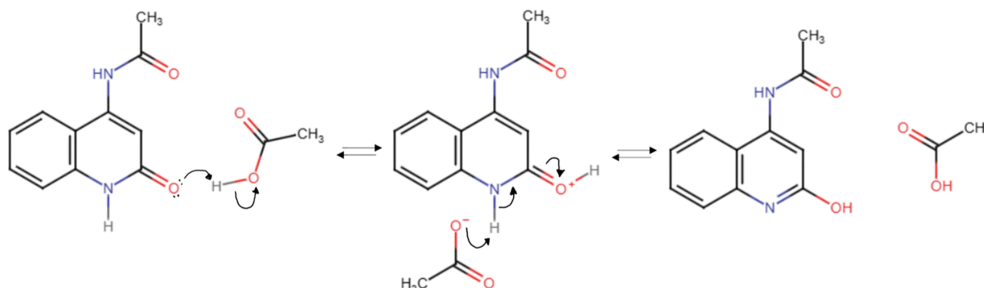


Fig. 7: Proposed acid-catalyzed tautomerization mechanism.

While the transition states for the individual steps could not be located (likely due to the flatness of the potential energy surface and the instability of the protonated intermediate), geometry optimizations successfully identified seven distinct minima corresponding to stable complexes between the acid (or acetate) and the different tautomers (Figure 8). The Cartesian coordinates and absolute energies of these minima are provided in the Supporting Information.

A striking observation is that five out of the seven minima involve stabilization of the 2-hydroxy tautomer (T2) by interaction with acetic acid/acetate, while only two stabilize the quinolone (T1). This suggests that the product (T2) has a greater capacity to form stabilizing hydrogen bonds with the medium. Most notably, one complex (highlighted in a black box in Figure 8) shows the acetic acid molecule acting as an "anchor", simultaneously forming hydrogen bonds with both the 2-OH group and the carbonyl oxygen of the acetamido group. This dual interaction is unique to the acetamido system and provides significant extra stabilization to the T2 form. Furthermore, this interaction locks the O-H bond in an orientation away from N1, physically preventing the intramolecular proton transfer that would lead back to T1. This structure offers a compelling explanation for the exclusive observation of the 4-acetamido-2-hydroxyquinoline: once formed, it is stabilized by specific, strong interactions with the acetic acid solvent, and the barrier for the reverse reaction is further increased by this conformational lock.

Ongoing molecular dynamics simulations in our group, to be reported in a future contribution, indicate that the 4-acetamido-2-hydroxyquinoline forms a significantly larger number of stabilizing hydrogen bonds with the surrounding water molecules compared to its quinolone counterpart, while the 4-amino system exhibits a much smaller difference in hydrogen-bonding propensity between the two tautomers. These

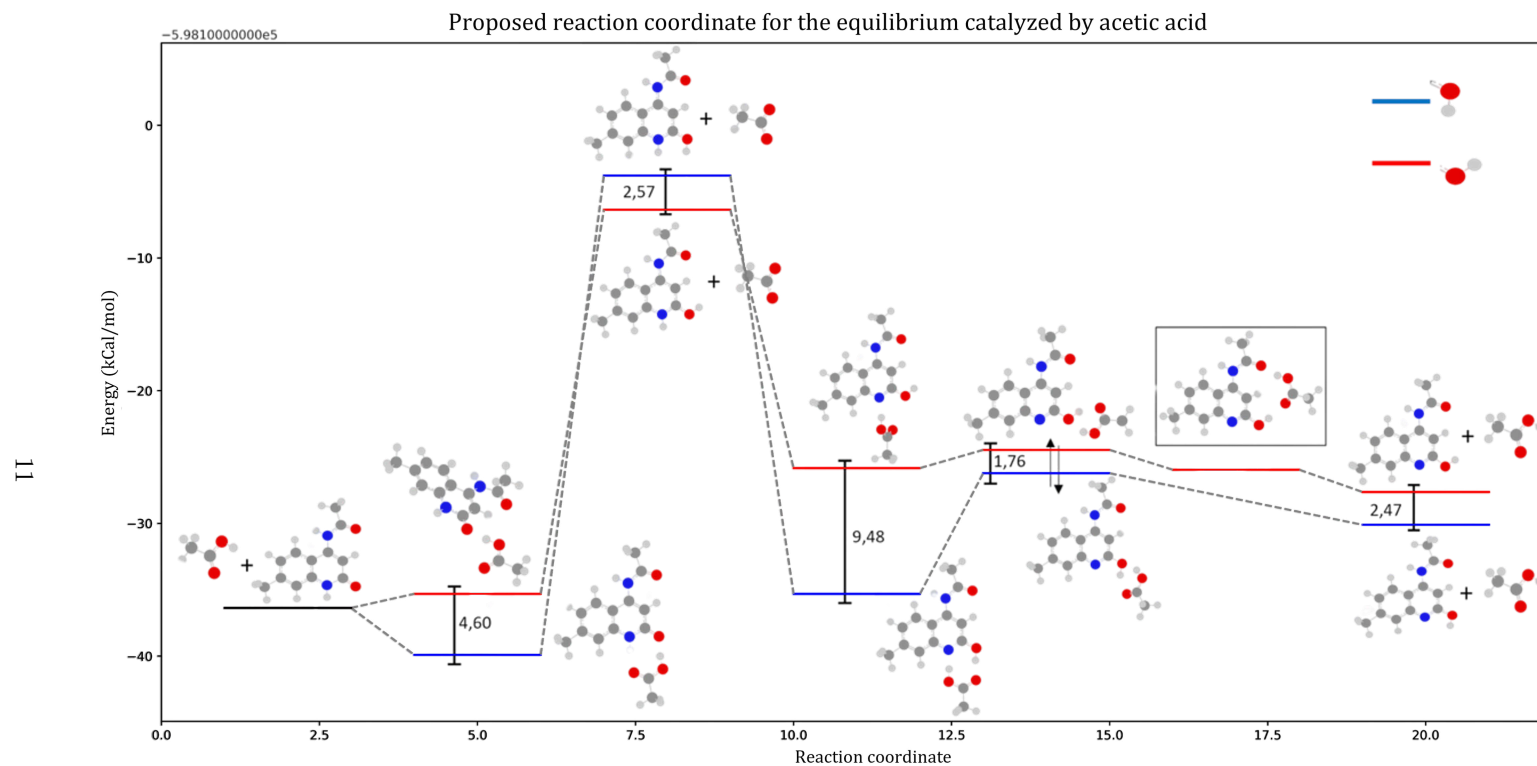


Fig. 8: Seven minimum energy structures identified for complexes of the 4-acetamido system with acetic acid/acetate. Two main pathways are highlighted: one leading to T2(a) (blue frames) and one to T2(b) (red frames). The structure in the black box shows the acetic acid molecule acting as an "anchor", simultaneously forming hydrogen bonds with both the 2-OH group and the carbonyl oxygen of the acetamido group.

preliminary results further support the notion that specific solute–solvent interactions play a decisive role in favoring the enol form in the acetamido system, and are consistent with the experimental observation that only the 2-hydroxy tautomer is isolated.

4 Conclusion

In this work, we have used DFT calculations to unravel the origin of the different tautomeric behavior of 4-amino and 4-acetamido-2-hydroxyquinolines. Our key findings are:

- A benchmark study against ^{13}C NMR data validated the MPW1PW91/6-31G(d,p) level of theory as a reliable method for modeling these quinoline systems.
- Both tautomeric equilibria are thermodynamically biased towards the quinolone form. The experimental observations cannot be explained by thermodynamic stability alone.
- The 4-acetamido system exhibits a significantly higher kinetic barrier for the reverse tautomerization ($\text{T2} \rightarrow \text{T1}$) compared to the 4-amino system. This kinetic trapping is a primary factor favoring the exclusive observation of the 2-hydroxy tautomer.
- Global hardness analysis reveals that in the 4-acetamido system, the 2-hydroxy tautomer (T2) is consistently harder (less polarizable) than the quinolone (T1), especially in polar solvents. This increased electronic rigidity further stabilizes T2 and contributes to its reduced tendency to tautomerize.
- The orientation of the flexible acetamido group profoundly influences the molecular dipole moment and the energy gap between tautomers, highlighting its conformational role.
- Explicit interaction models with acetic acid revealed multiple stable complexes. The 2-hydroxy tautomer forms more and stronger complexes with the solvent. A key structure involving dual hydrogen bonds between acetic acid and both the 2-OH and the acetamido group provides specific stabilization and physically hinders the return to the quinolone form.

Our results demonstrate that the exclusive formation of 4-acetamido-2-hydroxyquinoline under the reported synthetic conditions is a consequence of a combination of factors: a higher kinetic barrier for its reversion, increased global hardness (electronic rigidity) of the product, and specific, stabilizing interactions with the acetic acid medium that preferentially solvate the product and lock its conformation. This study underscores the importance of considering not only intrinsic molecular properties but also explicit solvent and substituent effects in understanding and predicting tautomeric preferences.

Supplementary information. The online version of this article contains supplementary material, which includes: details of the 30 quinolines used for benchmarking (groups I–IV, Table S1) together with the complete statistical results for all six functional/basis set combinations (Tables S2–S4) and the corresponding linear regression plots (Figures S2–S3); full IRC profiles for both tautomeric systems in all solvents and with both basis sets, bar graphs of the activation and reaction free energies (Figures S5–S6), and the numerical energy data (Tables S5–S6); Cartesian coordinates and absolute energies (electronic energy, zero-point correction, thermal correction to Gibbs free energy) for all optimized structures, including the seven minima corresponding to complexes with acetic acid; and Wiberg bond indices for selected bonds, displayed both as molecular diagrams (Figures S7–S10) and as a numerical table (Table S5).

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Declarations

- **Ethics, Consent to Participate, and Consent to Publish declarations:** not applicable.
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- **Conflict of interest:** The authors declare no competing interests.
- **Author contribution:** C.N.R.: Investigation, Formal analysis, Writing – original draft. L.G.: Conceptualization, Methodology, Supervision, Writing – review & editing. G.C.: Conceptualization, Validation, Supervision, Writing – review & editing.
- **Data availability:** The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. The Supplementary Information provides the key optimized coordinates and energies.

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