Supplementary Information for

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

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Contents

1 Benchmarking Data

1.1 Molecules used for NMR validation

The 30 quinoline derivatives were divided into four groups (I–IV) according to their substitution patterns (Table S1). The structures of a representative molecule from each group are shown in Fig. S1.

Table S1: Substituents (R) for each quinoline group.

Group	Substituents (position)
I	6-Br, 6-CH_3, 6-NO_2, 6-OCH_3, 7-CH_3, 7-Cl, 7-OCH_3, 8-CH_3, 8-Cl, 8-CN, 8-OCH_3
II	6-Br, 6-CH_3, 6-OCH_3, 7-CH_3, 7-Cl, 7-OCH_3, 8-CH_3, 8-Cl, 8-OCH_3
III	6-Br, 6-CH_3, 6-OCH_3, 7-CH_3, 7-Cl, 8-CH_3, 8-Cl, 8-OCH_3
IV	6-Br, 6-CH_3

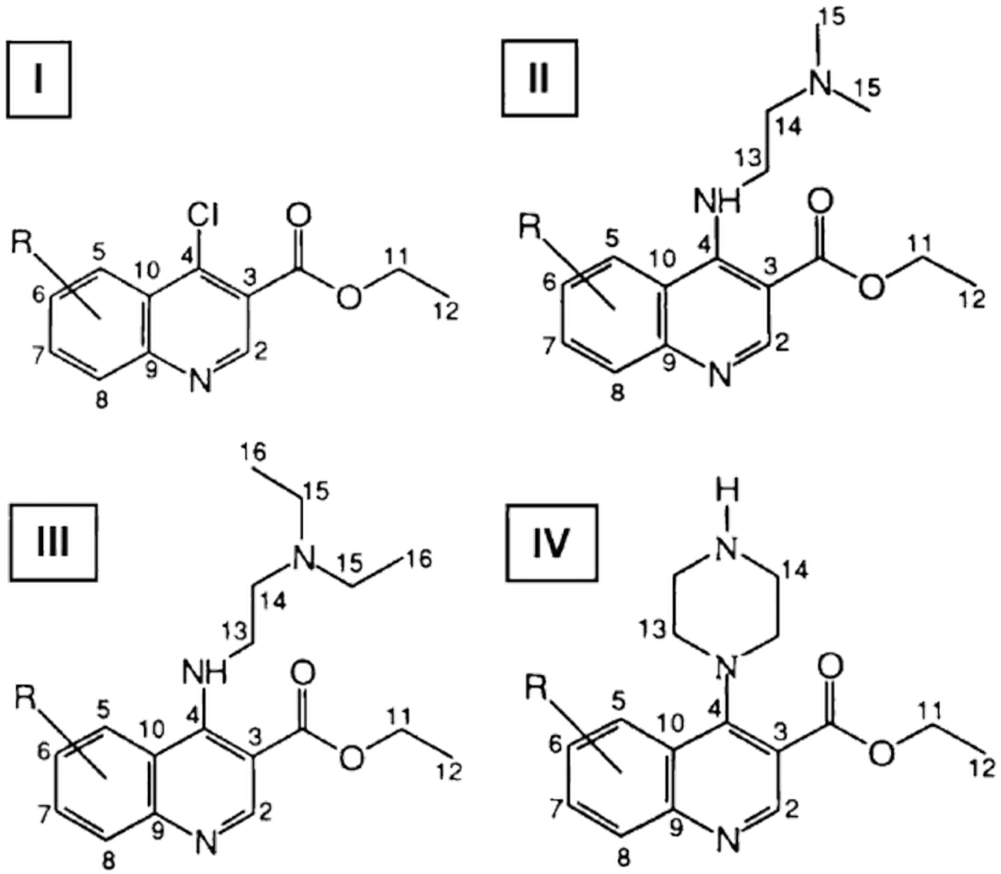

Figure S1: Representative structures from groups I–IV. The full list is provided in Table S1.

1.2 Statistical analysis methodology

Once linearity among the data sets was established, linear regression provides an equation with two useful parameters. The first is the slope of the line, which is a quantitative indicator of the systematic error of the computational method (a slope of exactly -1 would indicate zero systematic error). Therefore, the slope can be used to "adjust" the results so that the systematic error is eliminated. The second parameter is the intercept, which provides an alternative to the calculation of the shielding constant for the reference compound (e.g., tetramethylsilane, TMS), the traditional approach in NMR calculations.

A correlation coefficient very close to 1 is not the sole proof that the computational methods are adequate for simulating and interpreting ^{13}C NMR chemical shifts of organic compounds. It should be taken as a first measure, to be complemented with other parameters to evaluate the linear regression model and obtain valid conclusions about its goodness of fit. Following this approach, the mean absolute error (MAE) and mean squared error (MSE) were calculated for each data series as complementary measures.

Let $y = mx + b$ be the regression line equation, where:

$$\delta_{\text{calc}} = m \cdot \sigma_{\text{exp}} + b$$

- δ_{calc}: calculated isotropic shielding constant. - σ_{exp}: experimental chemical shift.

From here, σ_{calc} is defined as the result of subtracting the TMS reference shielding from the isotropic shielding of each carbon. The reference value for TMS (182.466 ppm) is the default used by Gaussian 09, calculated at the B3LYP/6-311+G(2d,p) GIAO level.

$$\sigma_{\text{calc}} = \delta_{\text{TMS}} - \delta_{\text{calc}}$$

The absolute and squared errors for each pair of data are:

$$\text{AE} = |\sigma_{\text{exp}} - \sigma_{\text{calc}}| \qquad \text{and} \qquad \text{SE} = (\sigma_{\text{exp}} - \sigma_{\text{calc}})^2$$

The mean values (MAE, MSE) are obtained by summing the errors for all signals (carbons of all molecules) and dividing by the total number of data points, for each functional/basis set combination.

In addition to these parameters, as reported by Rangel (2019), "calculating chemical shifts by direct comparison with a single TMS value has drawbacks", because σ_{calc} is obtained from a reference shielding calculated with a functional and basis set that are not equivalent to those used in this study. Therefore, a *corrected shift* was proposed based on the parameters b and m of each line (the intercept b acts as an alternative shielding constant for the reference compound, and m as an adjustment factor):

$$\sigma_{\text{corr}} = \frac{\delta_{\text{calc}} - b}{m}$$

With σ_{corr}, the corrected errors are defined:

$$\text{AE}_{\text{corr}} = |\sigma_{\text{exp}} - \sigma_{\text{corr}}| \qquad \text{and} \qquad \text{SE}_{\text{corr}} = (\sigma_{\text{exp}} - \sigma_{\text{corr}})^2$$

1.3 Results of the full analysis (all carbons)

The linear regression plots for all six functional/basis set combinations are shown in Figure S2.

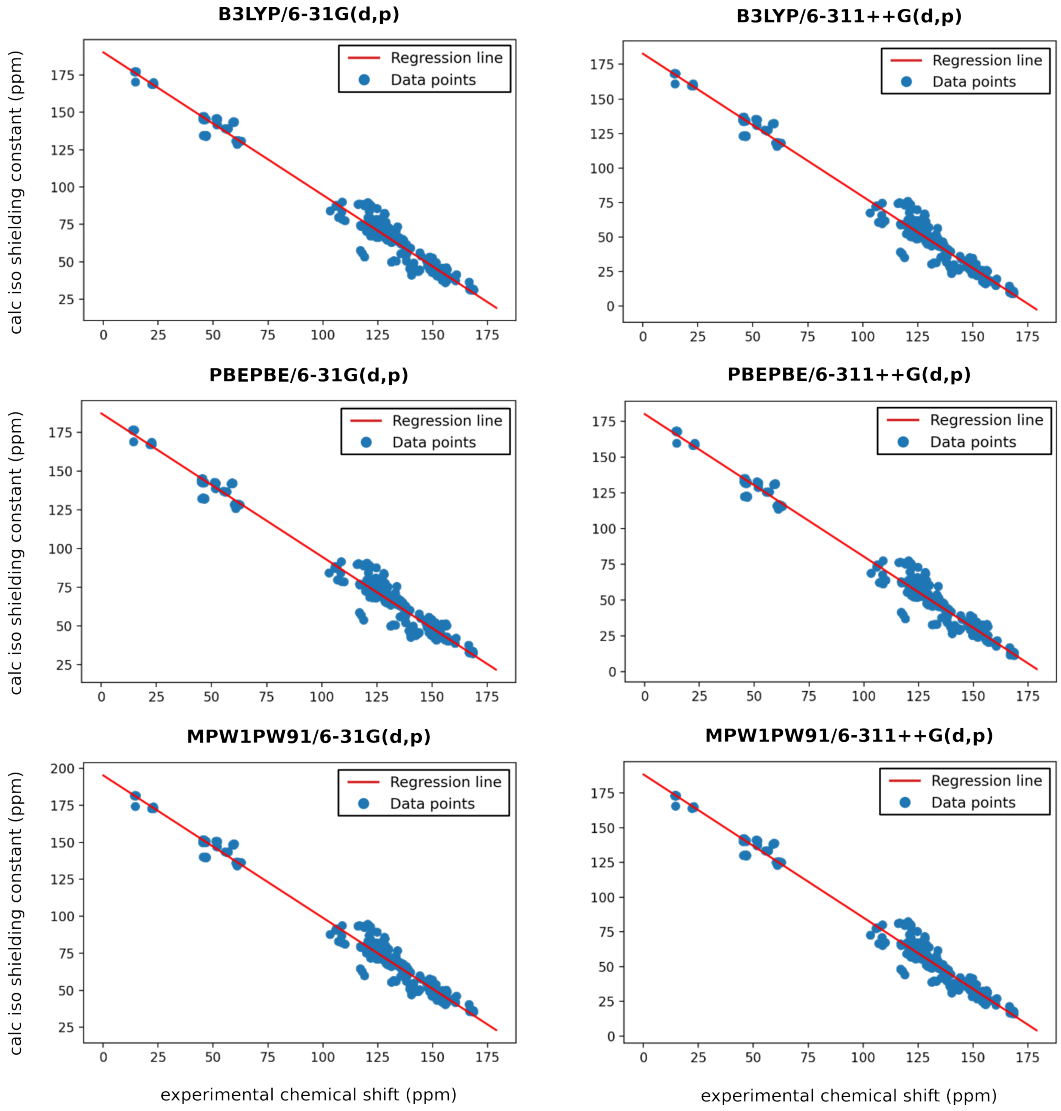

Figure S2: Linear regression plots for the six functional/basis set combinations (all carbon atoms). Experimental chemical shifts (σ_{exp}) versus calculated isotropic shielding constants (σ_{calc}).

Table S2 summarizes the parameters obtained for the six functional/basis set combinations studied. It can be observed that when σ_{calc} is corrected with the parameters b and m, the errors decrease notably, confirming the bias introduced by using a single TMS value. Taking the **corrected mean errors** and the **coefficient** R^2 as reference, the pair **MPW1PW91/6-31G(d,p)** shows the best linear correlation and the smallest MSE_{corr}. However, the same functional with the 6-311++G(d,p) basis gives the smallest MAE_{corr}. The differences between the two basis sets for the MPW1PW91 functional are less than or approximately 1% for all parameters.

Table S2: Results of the statistical correlation of experimental ^{13}C NMR data with theoretical values calculated for the six functional/basis set pairs.

Functional	Basis	m	b (ppm)	R^2	MAE (ppm)	MSE (ppm^2)	MAE$_{corr}$ (ppm)	MSE$_{corr}$ (ppm^2)
B3LYP	B1	-0.9545	190.11	0.9858	12.94	194.45	3.73	31.05
B3LYP	B2	-1.0349	182.74	0.9861	5.43	48.38	3.59	30.51
PBEPBE	B1	-0.9240	187.19	0.9837	13.50	217.13	4.10	35.80
PBEPBE	B2	-0.9961	180.20	0.9844	4.40	37.41	3.98	34.30
MPW1PW91	**B1**	-0.9623	**195.27**	**0.9871**	17.04	318.35	**3.57**	**28.15**
MPW1PW91	B2	-1.0296	188.43	0.9871	**4.61**	**38.91**	3.53	28.22

B1 = 6-31G(d,p); B2 = 6-311++G(d,p). The best values in each column are shown in bold.

1.4 Analysis restricted to quinoline ring carbons

Due to the absence of a uniform result (no functional/basis set was the best in all parameters), an additional analysis was performed focusing exclusively on the **quinoline ring carbons (positions 2 to 10)**. The experimental chemical shifts were compared with the calculated isotropic constants for those carbons. The parameters considered were the correlation coefficient R^2 and a **corrected mean relative error** (CMRE), defined as:

$$\mathrm{RE}_{corr} = \frac{|\sigma_{exp} - \sigma_{corr}|}{\sigma_{exp}} \times 100\%$$

The results are shown in **Table S3**.

Table S3: Results of the statistical analysis for the signals of carbons within the quinoline ring only.

Functional	Basis	m	b (ppm)	R^2	CMRE (%)
B3LYP	B1	-0.9805	193.44	0.8431	3.136
B3LYP	B2	-1.0675	187.05	0.8445	3.068
PBEPBE	B1	-0.9510	190.87	0.8250	3.303
PBEPBE	B2	-1.0226	183.98	0.8281	3.276
MPW1PW91	**B1**	-0.9885	**198.51**	**0.8580**	**3.028**
MPW1PW91	B2	-1.0629	192.71	0.8560	3.046

B1 = 6-31G(d,p); B2 = 6-311++G(d,p).

This specific comparison, which disregards substituents, is more representative for selecting the computational method that correctly describes the quinoline core. According to **Table S3**, the pair **MPW1PW91/6-31G(d,p)** is the most appropriate, as it presents the best R^2 and the smallest CMRE.

Nevertheless, the differences between MPW1PW91/6-31G(d,p) and MPW1PW91/6-311++G(d,p) remain below 1%. Therefore, it was decided to use both basis sets for the subsequent calculations in order to compare the trends.

Figure S3 displays the corresponding plots restricted to the quinoline ring carbons.

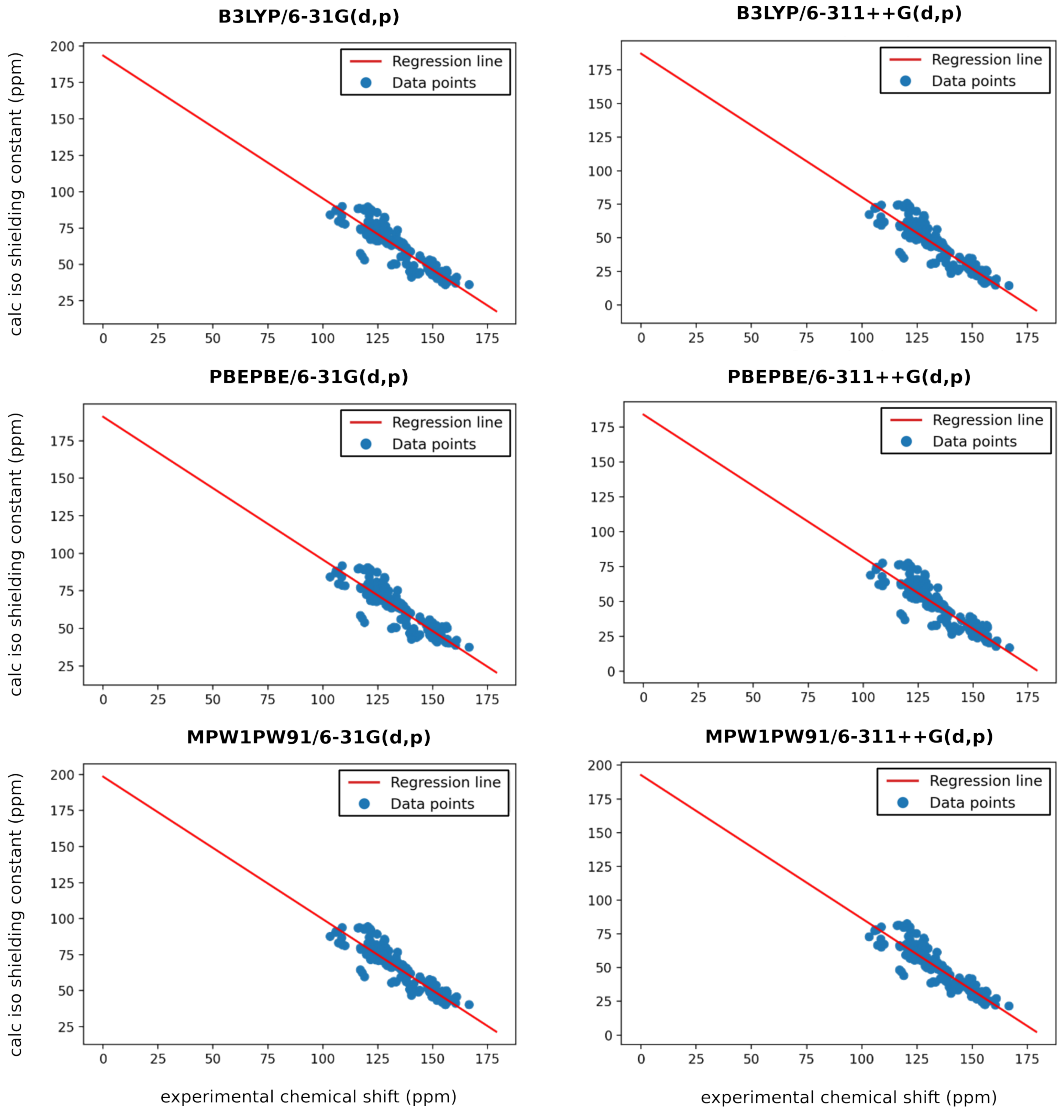

Figure S3: Linear regression plots for the six functional/basis set combinations, considering only the quinoline ring carbons (C2–C10). Experimental chemical shifts versus calculated isotropic shielding constants.

1.5 Example data for a representative molecule

As an illustration, **Figure S4** displays the theoretical ^{13}C NMR spectrum of **4-chloro-6-nitro-3-carboethoxyquinoline** computed at the B3LYP/6-31G(d,p) level. The spectrum was generated from the calculated isotropic shielding constants using the standard TMS reference. The assignment of the main signals is consistent with the data presented in Table S4.

Table S4 presents the experimental and calculated chemical shift data for this molecule. To enable automatic correlation between calculated isotropic shielding constants and ex-

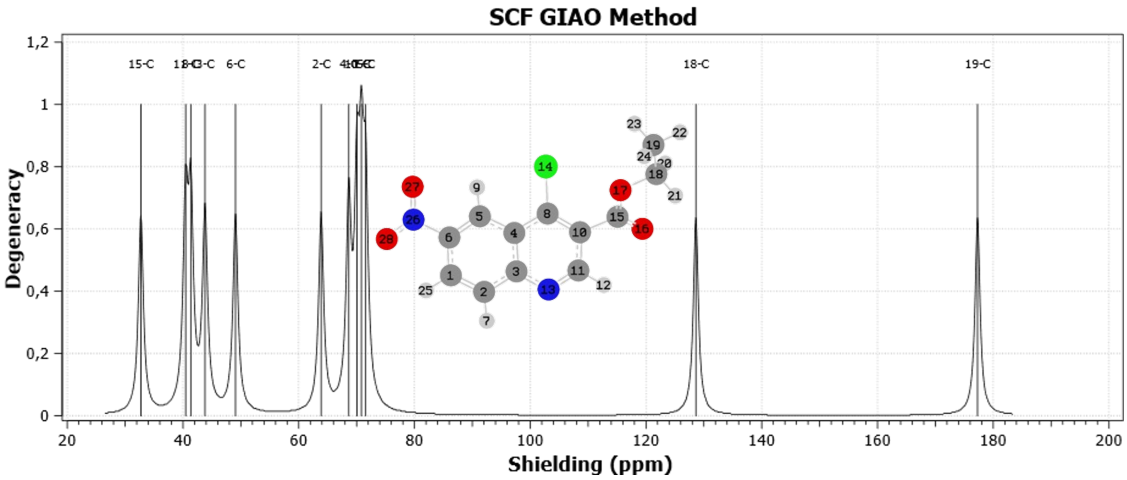

Figure S4: Theoretical ^{13}C NMR spectrum of 4-chloro-6-nitro-3-carboethoxyquinoline (B3LYP/6-31G(d,p)).

perimental chemical shifts across the 30 molecules, a custom algorithm was developed to enumerate the carbon atoms in each structure, ensuring that the indices matched those of the experimental data. In the full study, 180 tables were generated (6 functional/basis set combinations × 30 molecules).

Table S4: Data for 4-chloro-6-nitro-3-carboethoxyquinoline with B3LYP/6-31G(d,p).

Exp C#	σ_{exp} (ppm)	G09 C#	δ_{calc} (ppm)	σ_{calc} (ppm)	σ_{corr} (ppm)	AE (ppm)	SE (ppm^2)	AE_{corr} (ppm)	SE_{corr} (ppm^2)	RE_{corr} (%)
2	151.87	11	40.4635	142.0021	156.7769	9.8679	97.3755	–4.9069	24.0776	3.2310
3	124.59	10	70.0607	112.4049	125.7703	12.1851	148.4767	–1.1803	1.3932	0.9474
4	140.23	8	41.3526	141.1130	155.8455	–0.8830	0.7797	–15.6155	243.8425	11.1356
5	122.93	5	71.5652	110.9004	124.1942	12.0296	144.7113	–1.2642	1.5982	1.0284
6	148.74	6	49.0697	133.3959	147.7609	15.3441	235.4414	0.9791	0.9587	0.6583
7	128.15	1	70.8228	111.6428	124.9720	16.5072	272.4877	3.1780	10.1000	2.4799
8	131.26	2	63.8691	118.5965	132.2568	12.6635	160.3642	–0.9968	0.9936	0.7594
9	153.76	3	43.8032	138.6624	153.2782	15.0976	227.9375	0.4818	0.2322	0.3134
10	125.68	4	68.6398	113.8258	127.2589	11.8542	140.5221	–1.5789	2.4929	1.2563
=O	167.00	15	32.7228	149.7428	164.8862	17.2572	297.8110	2.1138	4.4682	1.2658
11	61.00	18	128.6212	53.8444	64.4213	7.1556	51.2026	–3.4213	11.7054	5.6087
12	14.50	19	177.2869	5.1787	13.4383	9.3213	86.8866	1.0617	1.1273	7.3223

Note: The 30 molecules produced 180 similar tables; only this representative example is shown.

2 Additional Energy Profiles

2.1 Intrinsic Reaction Coordinate (IRC) profiles

IRC calculations were performed not only for the gas phase reaction but also for a series of organic solvents with different polarities using the implicit solvent model based on the polarizable continuum model (CPCM). This model does not account for direct interactions between solute and solvent molecules but rather summarises the medium effect as a constant dielectric potential characteristic of each solvent. This analysis was carried out to study the behaviour of both equilibria as a function of the medium polarity.

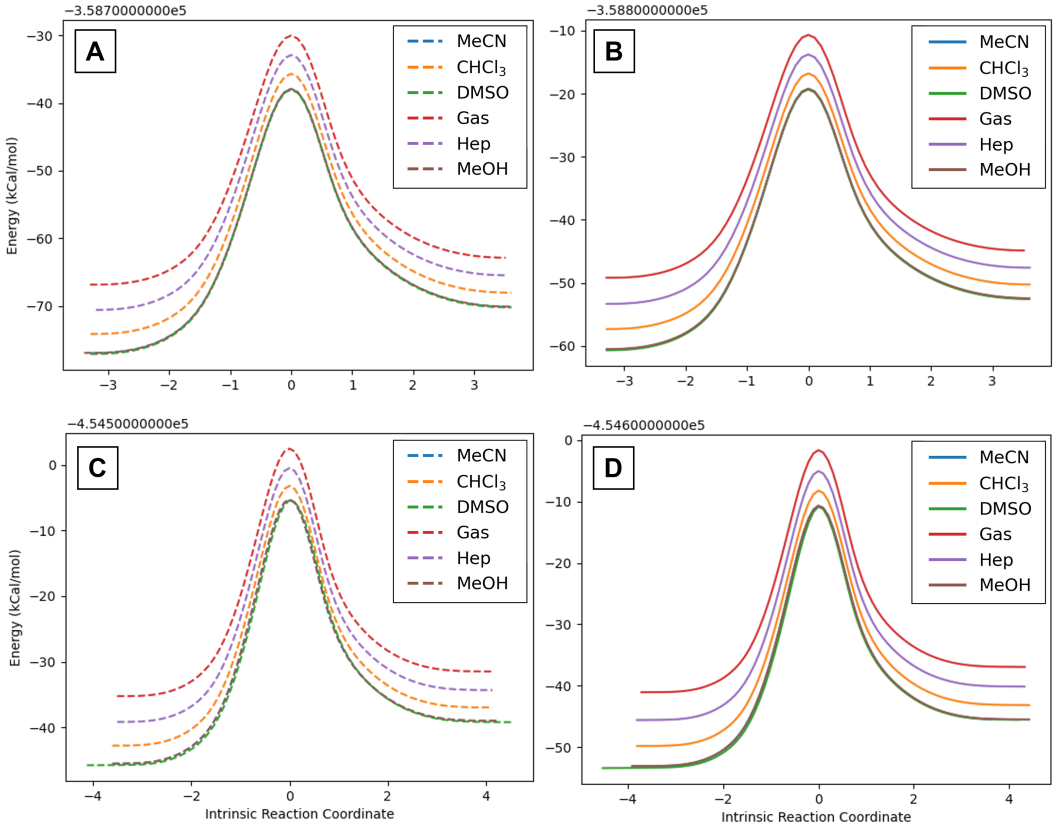

Figure S5: IRC profiles for the 4-amino and 4-acetamido systems using both basis sets (6-31G(d,p) and 6-311++G(d,p)). The four panels correspond to: (A) 4-amino/6-31G(d,p), (B) 4-amino/6-311++G(d,p), (C) 4-acetamido/6-31G(d,p), (D) 4-acetamido/6-311++G(d,p).

The main observation from the graphs in **Figure S5** is that the trends of the four energy diagrams are very similar to each other. For solvents with higher dielectric constants, the equilibrium is more stabilised in energy, which is consistent with the proposal of a transition state involving the transfer of a positively charged proton.

For the same equilibrium, when comparing the graphs obtained with the two different basis sets, the only noticeable difference corresponds to the limits of the y-axis in the plots, with more negative energies obtained for the larger basis set (as expected). Regarding the

separation of curves by solvent, the width of the observed peak and the number of steps on the x-axis, the two graphs for each basis set show the same behaviour.

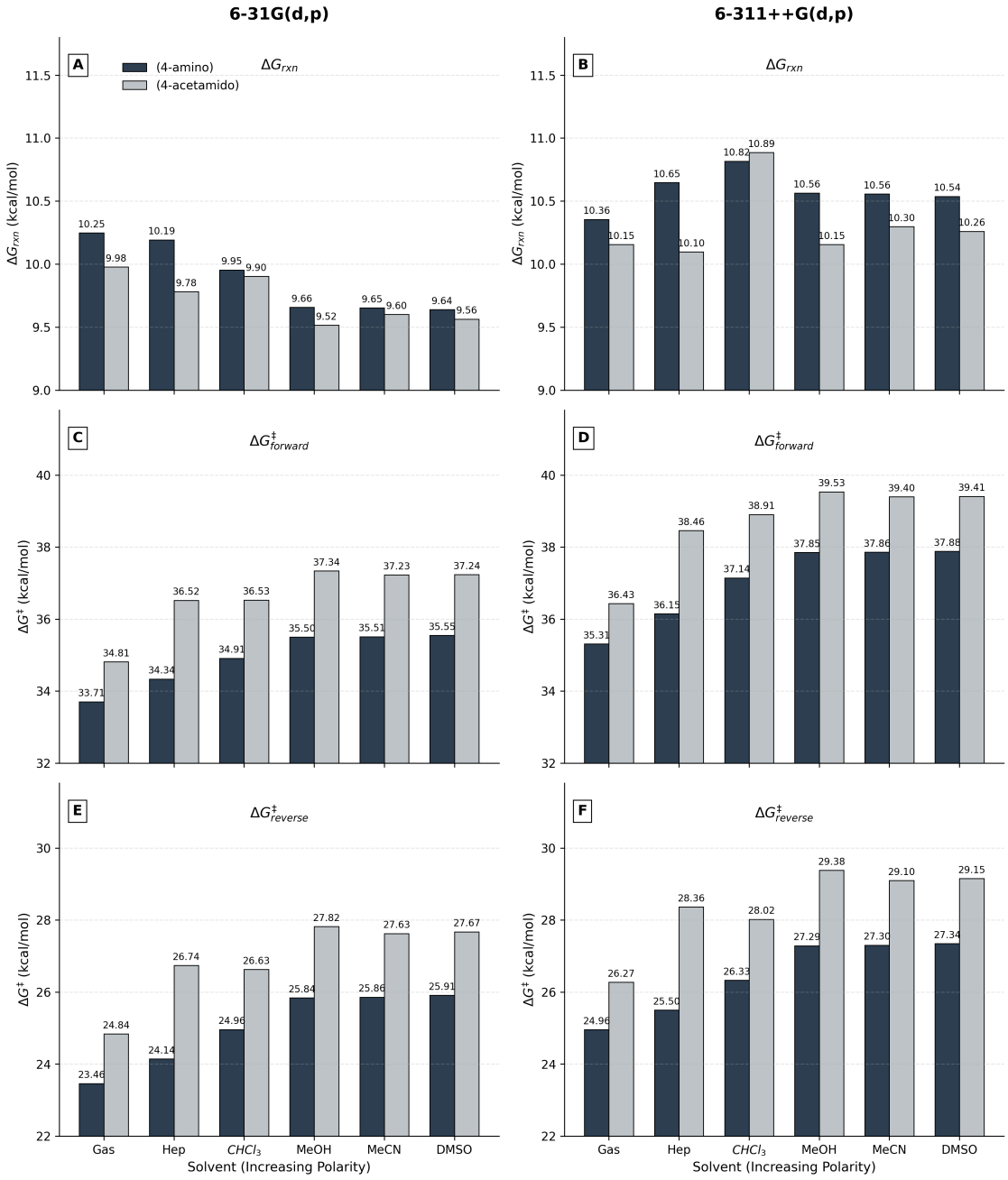

Figure S6: Bar graphs of (A and B) ΔG_{rxn}, (C and D) forward activation barriers ($\Delta G^{\ddagger}$, T1→T2), and (E and F) reverse activation barriers ($\Delta G^{\ddagger}$, T2→T1) for the 4-amino (dark gray) and 4-acetamido (light gray) systems. For each system, left-side bars correspond to the 6-31G(d,p) basis set and right-side bars to 6-311++G(d,p). Solvents are arranged from left to right: gas, heptane, $CHCl_3$, MeOH, MeCN, DMSO.

To better visualise differences in the energy values from these plots, bar graphs were

generated for ΔG_{rxn} (the difference in Gibbs free energy between T2 and T1), $\Delta G^{\ddagger}$ (forward direction, T1 $\rightarrow$ T2), and $\Delta G^{\ddagger}$ (reverse direction, T2 $\rightarrow$ T1). These bar graphs are compiled in **Figure S6**. The underlying energy data are summarised in Tables S5 and S6.

Table S5: Electronic energy plus thermal correction to Gibbs free energy (kcal mol^{-1}, 298 K) for the 4-amino tautomeric system.

		Solvent					
Structure	Basis	Gas	Heptane	$CHCl_3$	MeOH	MeCN	DMSO
T1	B1	-358415.5	-358419.1	-358422.7	-358425.6	-358425.7	-358425.8
	B2	-358498.6	-358502.7	-358506.8	-358510.0	-358510.1	-358510.2
T2	B1	-358405.2	-358408.9	-358412.7	-358416.0	-358416.0	-358416.2
	B2	-358488.2	-358492.0	-358496.0	-358499.5	-358499.5	-358499.7
TS	B1	-358381.8	-358384.8	-358387.8	-358390.1	-358390.2	-358390.2
	B2	-358463.3	-358466.5	-358469.7	-358472.2	-358472.2	-358472.3
ΔG_{rxn}	B1	10.248	10.193	9.954	9.658	9.653	9.639
	B2	10.355	10.647	10.817	10.564	10.557	10.538
$\Delta G^{\ddagger}$ (forward)	B1	33.707	34.336	34.912	35.499	35.513	35.547
	B2	35.311	36.146	37.144	37.851	37.860	37.883
$\Delta G^{\ddagger}$ (reverse)	B1	23.459	24.143	24.958	25.840	25.860	25.908
	B2	24.956	25.498	26.327	27.287	27.303	27.345

B1 = 6-31G(d,p); B2 = 6-311++G(d,p).

Regarding the comparative analysis of the calculated energies, only positive values of ΔG_{rxn} were observed; therefore, for both equilibria studied, the IRC calculations indicate endergonic reactions that are not spontaneous in the proposed reaction direction. Based on the sign of this quantity, it is possible to predict which tautomer will predominate once equilibrium is established. According to the data, in both cases the quinolone tautomer is expected to be predominant. This is consistent with the experimental results for the synthesis of the non-acetylated aminoquinoline, but contrary to those reported for the synthesis of the acetylated aminoquinoline.

Concerning the $\Delta G^{\ddagger}$ (forward direction) values, it was observed that in all cases the energy for the equilibrium of the acetylated quinoline is considerably larger. This magnitude ($\Delta G^{\ddagger}$ in the forward direction) is directly related to the activation energy required to establish the equilibrium. Thus, it can be concluded that a higher barrier must be overcome for the tautomerisation of the 4-acetamido system compared to the 4-amino system.

Finally, analysis of the $\Delta G^{\ddagger}$ (reverse direction) values shows very little variation across all results, with a slight tendency to decrease as the solvent polarity decreases. This magnitude refers to the relative stability gained by the final tautomer after crossing the transition state. It can be seen that for the non-acetylated quinoline, the energy barrier is smaller, making it feasible for both species to coexist in equilibrium in the medium. In contrast, for the acetylated system this is disfavoured both by the larger barrier height and by the possible energy gain after the reaction occurs.

Table S6: Electronic energy plus thermal correction to Gibbs free energy (kcal mol^{-1}, 298 K) for the 4-acetamido tautomeric system.

		Solvent					
Structure	Basis	Gas	Heptane	$CHCl_3$	MeOH	MeCN	DMSO
T1	B1	-454094.4	-454099.0	-454101.8	-454104.7	-454104.7	-454104.8
	B2	-454201.0	-454206.4	-454210.1	-454213.3	-454213.2	-454213.3
T2	B1	-454084.4	-454089.3	-454091.9	-454095.2	-454095.1	-454095.2
	B2	-454190.9	-454196.3	-454199.2	-454203.1	-454202.9	-454203.0
TS	B1	-454059.5	-454062.5	-454065.3	-454067.4	-454067.4	-454067.5
	B2	-454164.6	-454168.0	-454171.2	-454173.7	-454173.8	-454173.9
ΔG_{rxn}	B1	9.978	9.781	9.903	9.516	9.601	9.564
	B2	10.155	10.097	10.886	10.155	10.298	10.260
$\Delta G^{\ddagger}$ (forward)	B1	34.813	36.520	36.530	37.336	37.228	37.237
	B2	36.429	38.458	38.905	39.534	39.396	39.410
$\Delta G^{\ddagger}$ (reverse)	B1	24.836	26.739	26.627	27.820	27.627	27.672
	B2	26.274	28.361	28.019	29.379	29.098	29.150

B1 = 6-31G(d,p); B2 = 6-311++G(d,p).

3 Cartesian Coordinates and Absolute Energies

All structures were optimised at the MPW1PW91/6-31G(d,p) level (and re-optimised with 6-311++G(d,p) for the main systems). Energies (E, G_{298}, ZPE) are in Hartrees; coordinates in Ångströms. For each structure, we report the total electronic energy (E), the thermal correction to Gibbs free energy (G_{corr}) and the zero-point vibrational energy (ZPE) as obtained from frequency calculations.

3.1 4-Amino system (MPW1PW91/6-31G(d,p), gas phase)

3.1.1 T1 : 4-amino-7-methyl-2-quinolone

```
E = -571.7371753 Hartree
Zero-point correction = 0.186917 Hartree
Thermal correction to Energy = 0.197960 Hartree
Thermal correction to Gibbs Free Energy = 0.149984 Hartree

Coordinates (Å):
C     5.228664   -0.983561   -0.043021
C     4.841155    0.345796    0.002019
C     3.486648    0.706615    0.055580
C     2.488900   -0.289750    0.045444
C     2.898552   -1.631790    0.023847
C     4.234337   -1.976892   -0.022950
H     5.593274    1.129461    0.002877
```

```
C     1.099386    0.136595    0.074580
H     2.156138   -2.420772    0.075681
C     0.798597    1.466032    0.163191
C     1.807494    2.497209    0.207640
N     3.116874    2.022968    0.126347
H     4.521448   -3.023080   -0.034862
H    -0.228295    1.810309    0.186266
C     6.680550   -1.365057   -0.103992
H     7.329591   -0.489069   -0.055756
H     6.947569   -2.028899    0.723342
H     6.906591   -1.899966   -1.031427
O     1.599681    3.700995    0.285487
N     0.119051   -0.830224    0.061289
H    -0.817168   -0.488658   -0.085536
H     0.316935   -1.661851   -0.470474
H     3.823537    2.742999    0.143795
```

3.1.2 TS – Transition state

```
E = -571.6786251 Hartree
Zero-point correction = 0.181733 Hartree
Thermal correction to Energy = 0.192552 Hartree
Thermal correction to Gibbs Free Energy = 0.145188 Hartree

Coordinates (Å):
C     2.454386   -0.394912   -0.039752
C     1.323714   -1.180673   -0.134970
C     0.035487   -0.613039   -0.092911
C    -0.114922    0.792438    0.066353
C     1.053614    1.575325    0.141006
C     2.304253    1.002957    0.092608
H     1.403349   -2.256178   -0.250376
C    -1.453568    1.341367    0.129837
H     0.981756    2.656085    0.208656
C    -2.553631    0.513619   -0.005298
C    -2.319122   -0.862526   -0.179781
N    -1.075929   -1.378350   -0.206890
H     3.187113    1.631412    0.147207
H    -3.565852    0.894493    0.036731
C     3.828414   -1.000371   -0.082577
H     4.372300   -0.804124    0.846591
H     3.786281   -2.081208   -0.225859
H     4.420547   -0.573409   -0.897486
O    -3.111983   -1.864345   -0.319137
H    -1.868883   -2.378619   -0.346509
```

```
N    -1.614782    2.691391    0.282973
H    -2.543295    3.012473    0.499752
H    -0.885339    3.204108    0.746519
```

3.1.3 T2: 4-amino-2-hydroxy-7-methylquinoline

```
E = -571.7206553 Hartree
Zero-point correction = 0.186252 Hartree
Thermal correction to Energy = 0.197344 Hartree
Thermal correction to Gibbs Free Energy = 0.149807 Hartree

Coordinates (Å):
C     5.222481   -0.969143   -0.051178
C     4.833582    0.349082    0.027745
C     3.471547    0.727774    0.100310
C     2.480736   -0.293102    0.073764
C     2.892658   -1.642837    0.011848
C     4.223819   -1.972997   -0.050465
H     5.564675    1.150190    0.043210
C     1.110408    0.122148    0.116979
H     2.156989   -2.440498    0.043685
C     0.847036    1.473218    0.222995
C     1.928119    2.383639    0.267263
N     3.189044    2.052679    0.197598
H     4.518964   -3.016972   -0.091332
H    -0.178678    1.829911    0.258259
C     6.672035   -1.357205   -0.126754
H     7.321312   -0.480631   -0.100504
H     6.949982   -2.008932    0.707404
H     6.885023   -1.907665   -1.048539
O     1.689059    3.710939    0.372699
H     0.740654    3.855251    0.434803
N     0.098088   -0.806942    0.097554
H    -0.825260   -0.450911   -0.086693
H     0.288939   -1.673765   -0.375809
```

3.2 4-Acetamido system (MPW1PW91/6-31G(d,p), gas phase, M1 conformer)

3.2.1 T1 : 4-acetamido-7-methyl-2-quinolone

```
E = -724.3554714 Hartree
Zero-point correction = 0.225213 Hartree
Thermal correction to Energy = 0.239486 Hartree
Thermal correction to Gibbs Free Energy = 0.183255 Hartree
```

Coordinates (Å):

C	2.997345	-0.702168	0.038438
C	2.486915	0.584965	-0.006458
C	1.104838	0.815077	-0.049737
C	0.203713	-0.269682	-0.065837
C	0.736355	-1.567206	0.007426
C	2.098319	-1.783042	0.053945
H	3.161597	1.436093	-0.002590
C	-1.217314	0.028180	-0.138516
H	0.068918	-2.420366	0.055505
C	-1.644956	1.320002	-0.157540
C	-0.732801	2.446378	-0.088731
N	0.611355	2.094174	-0.059130
H	2.480618	-2.796525	0.112375
H	-2.687539	1.577381	-0.272112
C	4.478672	-0.946747	0.077369
H	5.040237	-0.012624	0.129273
H	4.753484	-1.555547	0.943365
H	4.808421	-1.488172	-0.814441
O	-1.066357	3.622174	-0.086173
N	-2.086020	-1.058059	-0.222999
H	-1.757844	-1.866443	-0.732093
H	1.249120	2.876395	-0.037468
C	-3.373522	-1.260881	0.250006
O	-3.947843	-2.288781	-0.053678
C	-3.991429	-0.230603	1.158234
H	-3.258524	0.311931	1.755600
H	-4.558189	0.495843	0.569940
H	-4.695258	-0.755088	1.802967

3.2.2 TS – Transition state (4-acetamido)

E = -724.2953989 Hartree
Zero-point correction = 0.220209 Hartree
Thermal correction to Energy = 0.234178 Hartree
Thermal correction to Gibbs Free Energy = 0.178702 Hartree

Coordinates (Å):

C	2.960210	-0.771077	0.024038
C	2.497609	0.527291	0.090560
C	1.119196	0.808783	0.053794
C	0.175797	-0.249044	-0.073051
C	0.671997	-1.568709	-0.110821
C	2.022707	-1.824095	-0.068215

```
H     3.186932    1.359821    0.178786
C    -1.230435    0.084614   -0.137256
H    -0.014998   -2.407363   -0.144628
C    -1.645930    1.394841   -0.047404
C    -0.649112    2.384058    0.117880
N     0.656852    2.078728    0.153228
H     2.375939   -2.849568   -0.094909
H    -2.677664    1.690070   -0.158028
C     4.429800   -1.076984    0.060265
H     4.671165   -1.742501    0.894328
H     4.746171   -1.583324   -0.856698
H     5.026322   -0.169846    0.167488
O    -0.718256    3.660678    0.221295
H     0.596093    3.360746    0.253988
N    -2.122590   -0.962055   -0.335169
H    -1.785498   -1.751340   -0.867463
C    -3.439045   -1.163862    0.058511
O    -4.015149   -2.154754   -0.345394
C    -4.084206   -0.187625    1.006287
H    -3.375322    0.281688    1.688748
H    -4.595361    0.599547    0.445673
H    -4.839752   -0.738834    1.564200
```

3.2.3 T2 : 4-acetamido-2-hydroxy-7-methylquinoline

```
E = -724.3391699 Hartree
Zero-point correction = 0.224555 Hartree
Thermal correction to Energy = 0.238880 Hartree
Thermal correction to Gibbs Free Energy = 0.182866 Hartree

Coordinates (Å):
C     3.012621   -0.643499    0.043287
C     2.476268    0.623516    0.002914
C     1.079466    0.841847   -0.048216
C     0.210308   -0.285265   -0.076369
C     0.771997   -1.580860   -0.008865
C     2.132115   -1.753607    0.046278
H     3.109780    1.503622    0.014502
C    -1.192539   -0.022448   -0.160692
H     0.126581   -2.452051    0.029336
C    -1.616322    1.286204   -0.184976
C    -0.647645    2.320000   -0.105467
N     0.640280    2.126843   -0.052506
H     2.543706   -2.756439    0.103341
H    -2.664119    1.526890   -0.317081
```

```
C     4.496848   -0.867047    0.095653
H     5.042225    0.077692    0.112018
H     4.778113   -1.436342    0.986855
H     4.838538   -1.439719   -0.772105
O    -1.038167    3.612543   -0.108674
H    -1.998211    3.656784   -0.135800
N    -2.071609   -1.099702   -0.265711
H    -1.740094   -1.908019   -0.772778
C    -3.344789   -1.310335    0.234384
O    -3.931790   -2.332355   -0.065358
C    -3.942052   -0.287145    1.167138
H    -3.195339    0.256835    1.746017
H    -4.536521    0.434459    0.600132
H    -4.620795   -0.820207    1.831503
```

3.3 4-Acetamido system (MPW1PW91/6-311++G(d,p), gas phase, M2 conformer)

3.3.1 T1 : 4-acetamido-7-methyl-2-quinolone (M2)

```
E = -724.5257209 Hartree
Zero-point correction = 0.223202 Hartree
Thermal correction to Energy = 0.238036 Hartree
Thermal correction to Gibbs Free Energy = 0.178624 Hartree

Coordinates (Å):
C     3.228772   -0.864113   -0.016603
C     2.769460    0.439224    0.000015
C     1.398950    0.729695    0.003433
C     0.448389   -0.308998   -0.010257
C     0.934864   -1.625195   -0.026073
C     2.285189   -1.902269   -0.029318
H     3.477112    1.261940    0.010830
C    -0.959083    0.064570   -0.006339
H     0.256341   -2.471004   -0.035738
C    -1.327680    1.372892    0.011048
C    -0.354257    2.444317    0.026043
N     0.971236    2.029398    0.020483
H     2.620842   -2.932784   -0.041577
H    -2.365380    1.663187    0.013534
C     4.697545   -1.170373   -0.022302
H     5.296573   -0.259845    0.008704
H     4.972025   -1.785171    0.838774
H     4.976608   -1.727431   -0.920595
O    -0.621390    3.633490    0.041950
```

```
N    -1.876953   -0.983446   -0.022560
H    -1.487128   -1.908314   -0.036935
H     1.649454    2.776623    0.030249
C    -3.256862   -0.928354   -0.012917
O    -3.891129    0.100372    0.001232
C    -3.928616   -2.281867   -0.004270
H    -3.251388   -3.119135   -0.179452
H    -4.415250   -2.419187    0.963299
H    -4.707379   -2.284343   -0.766465
```

3.3.2 TS – Transition state (M2)

```
E = -724.4643568 Hartree
Zero-point correction = 0.218075 Hartree
Thermal correction to Energy = 0.232569 Hartree
Thermal correction to Gibbs Free Energy = 0.174763 Hartree

Coordinates (Å):
C     3.112817   -0.884000    0.124089
C     2.694022    0.427507    0.110970
C     1.333930    0.757584   -0.028379
C     0.356343   -0.264962   -0.160134
C     0.812877   -1.597385   -0.141920
C     2.145837   -1.901892   -0.004965
H     3.406027    1.238702    0.208373
C    -1.030963    0.128573   -0.302037
H     0.123250   -2.429702   -0.235123
C    -1.395130    1.454437   -0.307600
C    -0.358523    2.401864   -0.169839
N     0.927069    2.047158   -0.039804
H     2.459245   -2.939610    0.004666
H    -2.420977    1.764166   -0.413158
C     4.562587   -1.239697    0.271790
H     4.723470   -1.864106    1.154705
H     4.915475   -1.806619   -0.593957
H     5.184343   -0.349525    0.369112
O    -0.373319    3.682537   -0.138538
H     0.924853    3.336014   -0.006990
N    -1.961455   -0.895141   -0.432428
H    -1.589555   -1.827946   -0.419630
C    -3.336501   -0.812925   -0.558753
O    -3.948516    0.228090   -0.598905
C    -4.024420   -2.156478   -0.609374
H    -3.381159   -2.965072   -0.960390
H    -4.378874   -2.405777    0.393894
```

```
H    -4.893363   -2.075306   -1.259581
```

3.3.3 T2 : 4-acetamido-2-hydroxy-7-methylquinoline (M2)

```
E = -724.5207952 Hartree
Zero-point correction = 0.223208 Hartree
Thermal correction to Energy = 0.237832 Hartree
Thermal correction to Gibbs Free Energy = 0.180014 Hartree

Coordinates (Å):
C     3.237808   -0.846540   -0.017166
C     2.769028    0.445407   -0.006064
C     1.388416    0.740922    0.003628
C     0.451612   -0.326311    0.001775
C     0.950167   -1.646801   -0.009025
C     2.298147   -1.900806   -0.018349
H     3.451518    1.287402   -0.004342
C    -0.940769    0.024574    0.011387
H     0.280705   -2.500818   -0.010169
C    -1.295457    1.349640    0.022318
C    -0.258582    2.307080    0.023395
N     1.018306    2.048006    0.014459
H     2.649054   -2.926985   -0.026543
H    -2.326245    1.663130    0.029224
C     4.707231   -1.150389   -0.028077
H     5.301564   -0.236413   -0.019671
H     4.991187   -1.746987    0.843244
H     4.982494   -1.724848   -0.916948
O    -0.636962    3.596564    0.034269
H     0.175135    4.116036    0.033093
N    -1.872900   -1.009286    0.007970
H    -1.492775   -1.938712   -0.000949
C    -3.249955   -0.932418    0.022779
O    -3.867675    0.107781    0.032280
C    -3.945281   -2.273551    0.041819
H    -3.280337   -3.124724   -0.111219
H    -4.448163   -2.387599    1.003989
H    -4.713217   -2.274216   -0.731474
```

3.4 Acid-catalyzed mechanism structures (MPW1PW91/6-31G(d,p), CPCM-water)

For the study of the acid catalysis by acetic acid (HOAc) on 4-acetamido-7-methyl-2-quinolone (T1) and its enol tautomer (T2), two reaction pathways, denoted (a) and (b), have been considered. The initial complexes of T1 with HOAc are named Cpre(a) and Cpre(b). The inter-

mediates resulting from proton transfer (protonated T1 species) are designated as IntH(a) and IntH(b). Subsequently, several T2·HOAc complexes are formed: two for pathway (a) (Com1(a), Com2(a)) and three for pathway (b) (Com1(b), Com2(b), Com3(b)). In addition, T2 itself exists in two distinct forms depending on the orientation of its OH group: in pathway (a) the OH points toward the N1 atom, whereas in pathway (b) the OH is oriented outward. This nomenclature allows an unambiguous distinction of all species involved in each catalytic step.

3.4.1 Acetic acid (HOAc)

```
E = -229.0396607 Hartree
Zero-point correction = 0.062369 Hartree
Thermal correction to Energy = 0.066950 Hartree
Thermal correction to Gibbs Free Energy = 0.035004 Hartree

Coordinates (Å):
H      0.325240     0.295984     0.063826
O     -0.482809     2.420767    -0.123742
C     -1.166498     1.425429    -0.026439
O     -0.638212     0.195727     0.081451
C     -2.664264     1.389687    -0.009719
H     -3.058490     2.399114    -0.098754
H     -3.029474     0.773152    -0.833710
H     -3.013751     0.933854     0.919000
```

3.4.2 Acetate anion (OAc)

```
E = -228.5477964 Hartree
Zero-point correction = 0.048952 Hartree
Thermal correction to Energy = 0.053375 Hartree
Thermal correction to Gibbs Free Energy = 0.021264 Hartree

Coordinates (Å):
O     -0.541805     2.457686     0.014963
C     -1.143200     1.354888    -0.005125
O     -0.629565     0.207284     0.003777
C     -2.686793     1.399404    -0.016956
H     -3.068017     2.406519    -0.199475
H     -3.086344     0.718064    -0.774031
H     -3.072534     1.054575     0.948761
```

3.4.3 T1

```
E = -724.3775166 Hartree
Zero-point correction = 0.224746 Hartree
Thermal correction to Energy = 0.239347 Hartree
```

```
Thermal correction to Gibbs Free Energy = 0.181355 Hartree

Coordinates (Å):
C      3.230518    -0.857172    -0.000293
C      2.767860     0.447712    -0.000231
C      1.393749     0.729257    -0.000047
C      0.444849    -0.315201     0.000001
C      0.935205    -1.634595    -0.000165
C      2.288183    -1.902139    -0.000333
H      3.471812     1.273987    -0.000355
C     -0.963365     0.053473     0.000067
H      0.260134    -2.483187    -0.000311
C     -1.328355     1.369849     0.000080
C     -0.357283     2.437657     0.000057
N      0.963120     2.032293    -0.000011
H      2.629876    -2.931453    -0.000569
H     -2.368510     1.651808     0.000105
C      4.700917    -1.160255     0.000369
H      5.299143    -0.248123    -0.008229
H      4.978338    -1.741427     0.884522
H      4.976174    -1.757100    -0.873874
O     -0.636521     3.638879     0.000093
N     -1.884869    -0.985505     0.000145
H     -1.504668    -1.917312     0.000324
H      1.646439     2.776763    -0.000044
C     -3.262690    -0.922346    -0.000023
O     -3.891584     0.122721    -0.000292
C     -3.923726    -2.278806     0.000215
H     -3.631348    -2.853474    -0.882387
H     -3.632621    -2.852430     0.883919
H     -5.002867    -2.142966    -0.000630
```

3.4.4 Cpre(b)

```
E = -953.4337457 Hartree
Zero-point correction = 0.288397 Hartree
Thermal correction to Energy = 0.309054 Hartree
Thermal correction to Gibbs Free Energy = 0.234618 Hartree

Coordinates (Å):
C      3.614315    -2.582518     0.395759
C      2.566370    -2.442942    -0.497314
C      1.840462    -1.246064    -0.573750
C      2.156872    -0.151251     0.256932
C      3.229250    -0.312077     1.156256
```

```
C      3.937798    -1.491720     1.225797
H      2.294601    -3.264544    -1.152365
C      1.357080     1.053884     0.117991
H      3.531501     0.491581     1.817694
C      0.340870     1.101782    -0.799738
C      0.032385    -0.018984    -1.636562
N      0.805812    -1.133986    -1.470358
H      4.758141    -1.580746     1.929475
H     -0.254325     1.993040    -0.912827
C      4.393768    -3.861586     0.487174
H      4.044022    -4.598233    -0.237164
H      5.457550    -3.682505     0.307682
H      4.307030    -4.297687     1.486562
O     -0.880220    -0.042412    -2.490635
N      1.670590     2.120845     0.942704
H      2.420295     1.973384     1.598318
C      1.087368     3.373061     0.998688
O      0.165897     3.718340     0.279574
C      1.703352     4.274866     2.037759
H      1.607372     3.838401     3.035148
H      2.767635     4.424709     1.839456
H      1.193357     5.235192     2.014116
H      0.578752    -1.920770    -2.062973
O     -3.932014     1.036674    -1.600668
C     -3.524195     2.016075    -2.197693
O     -2.329463     2.088072    -2.770554
C     -4.313824     3.284651    -2.373185
H     -5.288143     3.188560    -1.898776
H     -3.769774     4.124016    -1.934287
H     -4.439237     3.500531    -3.436518
H     -1.815745     1.229654    -2.629814
```

3.4.5 Cpre(a)

```
E = -953.4420355 Hartree
Zero-point correction = 0.288256 Hartree
Thermal correction to Energy = 0.308615 Hartree
Thermal correction to Gibbs Free Energy = 0.235580 Hartree

Coordinates (Å):
C      0.001621     3.434259     0.015334
C     -0.762266     2.281047     0.011362
C     -0.157430     1.014372     0.010251
C      1.247441     0.884319     0.013473
C      2.007815     2.070633     0.017380
```

```
C      1.405127     3.309608     0.018345
H     -1.845856     2.340204     0.008793
C      1.796591    -0.460044     0.011789
H      3.091437     2.041600     0.019192
C      0.955442    -1.541228     0.006476
C     -0.467860    -1.380634     0.003367
N     -0.948135    -0.106211     0.005662
H      2.020639     4.202621     0.021250
H      1.344449    -2.545904     0.004630
C     -0.637442     4.792282     0.015891
H     -1.726025     4.723795     0.015830
H     -0.330890     5.366102     0.895157
H     -0.330979     5.366617    -0.863104
O     -1.256653    -2.356780    -0.000987
N      3.177221    -0.581958     0.015457
H      3.700718     0.278037     0.025237
H     -1.974768    -0.007101     0.003453
C      3.945470    -1.729894     0.009661
O      3.475612    -2.854807    -0.001642
C      5.428915    -1.459061     0.021621
H      5.721845    -0.851111    -0.837940
H      5.714685    -0.917659     0.927083
H      5.957953    -2.408825    -0.011003
H     -2.789138    -2.226839    -0.004819
O     -3.808503    -2.290301    -0.008037
C     -4.375629    -1.107132    -0.006712
O     -3.756489    -0.046140    -0.002041
C     -5.874992    -1.168667    -0.011257
H     -6.217780    -1.715467    -0.892213
H     -6.222850    -1.716549     0.867062
H     -6.293714    -0.164933    -0.011730
```

3.4.6 IntH(b)

```
E = -724.8217820 Hartree
Zero-point correction = 0.237812 Hartree
Thermal correction to Energy = 0.252544 Hartree
Thermal correction to Gibbs Free Energy = 0.195332 Hartree

Coordinates (Å):
C      3.259796    -0.824577    -0.001050
C      2.771681     0.468169    -0.013155
C      1.391388     0.704440    -0.016817
C      0.460495    -0.356634    -0.008416
C      0.981848    -1.669075     0.003824
```

```
C      2.336924    -1.893589     0.007350
H      3.453904     1.311157    -0.019914
C     -0.945475    -0.030910    -0.012875
H      0.327924    -2.532635     0.010739
C     -1.341600     1.299565    -0.025222
C     -0.373677     2.299865    -0.033080
N      0.926870     1.999201    -0.028894
H      2.707335    -2.912374     0.016755
H     -2.389517     1.556727    -0.028659
C      4.732247    -1.101999     0.003687
H      5.316080    -0.181511    -0.009550
H      5.011968    -1.675337     0.891851
H      5.012973    -1.701653    -0.866531
O     -0.623065     3.594140    -0.044970
N     -1.849751    -1.057155    -0.004782
H     -1.470465    -1.990603     0.003410
H      1.587594     2.767304    -0.034875
C     -3.243342    -0.991039    -0.005734
O     -3.852978     0.059851    -0.014899
C     -3.901439    -2.342044     0.005603
H     -3.606981    -2.921304    -0.873257
H     -3.606155    -2.907127     0.893355
H     -4.980264    -2.206308     0.004960
H     -1.573165     3.768611    -0.047466
```

3.4.7 IntH(a)

```
E = -724.8180702 Hartree
Zero-point correction = 0.238126 Hartree
Thermal correction to Energy = 0.252800 Hartree
Thermal correction to Gibbs Free Energy = 0.195710 Hartree

Coordinates (Å):
C      3.230879    -0.851876     0.001940
C      2.752516     0.444111    -0.044257
C      1.374870     0.690945    -0.051400
C      0.435207    -0.359497    -0.012318
C      0.945331    -1.674990     0.034484
C      2.298955    -1.911426     0.041291
H      3.441606     1.281144    -0.075374
C     -0.968401    -0.019281    -0.022815
H      0.283818    -2.532195     0.066197
C     -1.346997     1.312501    -0.070321
C     -0.373341     2.308322    -0.107489
N      0.926392     1.995349    -0.097909
```

```
H      2.660133    -2.932935     0.077608
H     -2.384848     1.601030    -0.079316
C      4.701309    -1.140173     0.011062
H      5.291759    -0.224628    -0.028135
H      4.979051    -1.691270     0.913771
H      4.975834    -1.764791    -0.843399
O     -0.769510     3.563556    -0.152242
N     -1.882025    -1.037331     0.015095
H     -1.510890    -1.973416     0.048117
H      1.623626     2.729208    -0.125268
C     -3.274625    -0.959017     0.014016
O     -3.875720     0.095999    -0.022964
C     -3.943619    -2.304334     0.062746
H     -3.655879    -2.909222    -0.800961
H     -3.650952    -2.848122     0.964567
H     -5.021366    -2.160223     0.060709
H     -0.046015     4.203795    -0.176245
```

3.4.8 Com1(b)

```
E = -953.4191847 Hartree
Zero-point correction = 0.287917 Hartree
Thermal correction to Energy = 0.308545 Hartree
Thermal correction to Gibbs Free Energy = 0.235165 Hartree

Coordinates (Å):
C     -4.016725     0.772683     0.450272
C     -2.787902     1.244263     0.042011
C     -1.703043     0.373767    -0.206430
C     -1.877522    -1.026405    -0.036937
C     -3.144256    -1.492885     0.384970
C     -4.179688    -0.622309     0.621190
H     -2.624668     2.307021    -0.101262
C     -0.744095    -1.868544    -0.308672
H     -3.332277    -2.550224     0.535612
C      0.438211    -1.283598    -0.709976
C      0.488454     0.119958    -0.836726
N     -0.519617     0.926026    -0.602709
H     -5.140016    -1.009984     0.944442
H      1.303007    -1.894311    -0.921398
C     -5.166920     1.700403     0.714017
H     -4.891523     2.740773     0.535837
H     -6.018975     1.457302     0.072484
H     -5.510875     1.610199     1.748592
O      1.618383     0.733402    -1.224611
```

```
N     -0.887405    -3.237009    -0.157344
H     -1.798540    -3.560566     0.123511
C      0.055365    -4.230139    -0.336931
O      1.204208    -4.011303    -0.682760
C     -0.470295    -5.614603    -0.055483
H     -0.760962    -5.706853     0.994342
H     -1.349700    -5.832592    -0.666256
H      0.311636    -6.337747    -0.275791
H     -0.315007     2.594269    -0.715693
O     -0.316112     3.596749    -0.863053
C      0.313120     4.221442     0.123967
O      0.832718     3.652216     1.066487
C      0.309023     5.715325    -0.057303
H      0.778998     5.976247    -1.008107
H     -0.719277     6.082179    -0.092839
H      0.842284     6.193572     0.761594
H      2.314119     0.082082    -1.369232
```

3.4.9 Com2(b)

```
E = -953.4163918 Hartree
Zero-point correction = 0.288385 Hartree
Thermal correction to Energy = 0.308943 Hartree
Thermal correction to Gibbs Free Energy = 0.234556 Hartree

Coordinates (Å):
C      2.045530     3.298117     0.118839
C      0.814713     2.765297    -0.194759
C      0.596648     1.369046    -0.268426
C      1.684776     0.486026    -0.015752
C      2.942116     1.047906     0.308283
C      3.117105     2.408606     0.373385
H     -0.035669     3.409028    -0.394468
C      1.416942    -0.922302    -0.109517
H      3.801142     0.419769     0.518877
C      0.139623    -1.333449    -0.422469
C     -0.850094    -0.346701    -0.637653
N     -0.660114     0.944886    -0.576360
H      4.093143     2.810111     0.625759
H     -0.092479    -2.384503    -0.502911
C      2.266648     4.781239     0.197905
H      1.352576     5.334353    -0.023059
H      2.609038     5.072835     1.195310
H      3.038074     5.100406    -0.509245
O     -2.114032    -0.729249    -0.932870
```

```
H     -2.186918    -1.710854    -0.986765
N      2.459814    -1.810050     0.115835
H      3.357846    -1.398782     0.310723
C      2.437494    -3.187932     0.112307
O      1.434852    -3.846147    -0.113992
C      3.774386    -3.811041     0.428407
H      4.554845    -3.431854    -0.235554
H      4.067960    -3.579105     1.455646
H      3.694576    -4.889820     0.314686
H     -2.750417    -0.999610    -2.721630
O     -3.046621    -1.595878    -3.439663
C     -2.979695    -2.851576    -3.012112
O     -2.605192    -3.155435    -1.886439
C     -3.411025    -3.840771    -4.045560
H     -4.441908    -3.634982    -4.341026
H     -2.788374    -3.735936    -4.936315
H     -3.331032    -4.850213    -3.650216
```

3.4.10 Com3(b)

```
E = -953.4203255 Hartree
Zero-point correction = 0.288647 Hartree
Thermal correction to Energy = 0.309063 Hartree
Thermal correction to Gibbs Free Energy = 0.236105 Hartree

Coordinates (Å):
C     -4.330059    -0.532197     0.330093
C     -3.340825    -1.414972    -0.045067
C     -2.010333    -0.996158    -0.284331
C     -1.693404     0.386788    -0.150381
C     -2.712528     1.278705     0.256442
C     -3.991173     0.833675     0.487901
H     -3.555015    -2.472285    -0.162003
C     -0.344097     0.767920    -0.444834
H     -2.499474     2.330496     0.415207
C      0.558452    -0.200656    -0.800738
C      0.131487    -1.552216    -0.833938
N     -1.095924    -1.951202    -0.611017
H     -4.754418     1.538017     0.802437
H      1.575227     0.042774    -1.061169
C     -5.738752    -0.988324     0.580606
H     -5.843294    -2.064135     0.432218
H     -6.051438    -0.752741     1.602261
H     -6.438802    -0.482290    -0.090994
O      1.018838    -2.514781    -1.129496
```

```
H      1.918936    -2.136787    -1.130090
N      0.000866     2.120535    -0.387574
H     -0.765946     2.773400    -0.404347
C      1.244026     2.677167    -0.314469
O      2.287927     2.029335    -0.267271
C      1.274621     4.181648    -0.308917
H      1.763782     4.519416    -1.225290
H      0.290695     4.644955    -0.243201
H      1.886785     4.512289     0.531198
H      3.252963     0.723187     0.360994
O      3.918971     0.161111     0.822526
C      4.090982    -0.988467     0.194773
O      3.493802    -1.289629    -0.830444
C      5.097060    -1.869959     0.868046
H      6.055301    -1.350981     0.936286
H      4.770341    -2.085700     1.887575
H      5.213783    -2.796652     0.311559
```

3.4.11 Com1(a)

```
E = -953.4343276 Hartree
Zero-point correction = 0.287349 Hartree
Thermal correction to Energy = 0.307549 Hartree
Thermal correction to Gibbs Free Energy = 0.235199 Hartree

Coordinates (Å):
C      0.379351     3.302498     0.017158
C      1.010244     2.075972     0.011900
C      0.283013     0.865625     0.008282
C     -1.136423     0.904928     0.010111
C     -1.766537     2.169652     0.015493
C     -1.033408     3.332121     0.018907
H      2.093595     2.021005     0.010450
C     -1.831840    -0.357382     0.006318
H     -2.847393     2.258601     0.017073
C     -1.098462    -1.519992     0.001246
C      0.313726    -1.444576    -0.000187
N      0.986522    -0.308269     0.003122
H     -1.546938     4.287781     0.023015
H     -1.578301    -2.484640    -0.001668
C      1.159044     4.585374     0.021005
H      2.234213     4.400824     0.018961
H      0.915285     5.192946    -0.855483
H      0.917497     5.186325     0.902656
O      0.965788    -2.596222    -0.005148
```

```
H      1.956619    -2.455944    -0.005715
N     -3.217525    -0.342628     0.008004
H     -3.652611     0.565140     0.011961
C     -4.093744    -1.409299     0.004925
O     -3.735994    -2.575242     0.000190
C     -5.543485    -0.993527     0.007946
H     -5.773365    -0.395213     0.893250
H     -5.775267    -0.389269    -0.872816
H     -6.164392    -1.886503     0.005594
H      2.556280    -0.255620     0.000159
O      3.592159    -0.153002    -0.001588
C      4.182312    -1.318306    -0.005758
O      3.576116    -2.392088    -0.007375
C      5.679449    -1.245871    -0.009102
H      6.016940    -0.697916    -0.891381
H      6.021259    -0.692449     0.868009
H      6.106984    -2.245801    -0.007384
```

3.4.12 Com2(a)

```
E = -953.4191533 Hartree
Zero-point correction = 0.288247 Hartree
Thermal correction to Energy = 0.308823 Hartree
Thermal correction to Gibbs Free Energy = 0.234516 Hartree

Coordinates (Å):
C     -2.445725    -2.973591     0.097864
C     -1.142245    -2.590081    -0.130912
C     -0.765030    -1.230166    -0.217241
C     -1.758991    -0.223121    -0.060406
C     -3.092915    -0.632850     0.170703
C     -3.425585    -1.963644     0.247682
H     -0.358489    -3.330238    -0.254246
C     -1.326714     1.146031    -0.152111
H     -3.891192     0.091892     0.290184
C      0.004534     1.405694    -0.390324
C      0.881697     0.308966    -0.528600
N      0.549459    -0.952798    -0.450701
H     -4.458009    -2.246540     0.425517
H      0.373480     2.415195    -0.469291
C     -2.838155    -4.420283     0.186769
H     -1.975817    -5.076892     0.062346
H     -3.299465    -4.641937     1.153721
H     -3.573678    -4.674052    -0.582472
O      2.176237     0.608945    -0.769201
```

```
H      2.705368    -0.222532    -0.790861
N     -2.273937     2.148541     0.004660
H     -3.211997     1.844328     0.207225
C     -2.104911     3.514714    -0.064441
O     -1.034260     4.051621    -0.298394
C     -3.372433     4.291953     0.191163
H     -4.192846     3.936849    -0.436599
H     -3.677944     4.181715     1.235177
H     -3.186024     5.343623    -0.014941
H      3.492000     1.033876     0.530823
O      4.314303     0.838115     1.025390
C      4.771483    -0.349190     0.638993
O      4.213322    -1.038032    -0.203098
C      6.031721    -0.739645     1.342641
H      6.805226     0.006925     1.151144
H      5.858696    -0.762144     2.420507
H      6.362926    -1.715994     0.997680
```

3.4.13 T2(b)

```
E = -724.3632267 Hartree
Zero-point correction = 0.224093 Hartree
Thermal correction to Energy = 0.238740 Hartree
Thermal correction to Gibbs Free Energy = 0.180990 Hartree

Coordinates (Å):
C      2.256950    -1.983192    -0.000022
C      2.335762    -0.608269    -0.000023
C      1.182050     0.212055    -0.000013
C     -0.101725    -0.404587    -0.000002
C     -0.166662    -1.818020     0.000019
C      0.974289    -2.582473     0.000011
H      3.297913    -0.106537    -0.000024
C     -1.242982     0.467483     0.000005
H     -1.119470    -2.337010     0.000072
C     -1.034264     1.829576     0.000025
C      0.296645     2.307471     0.000019
N      1.369914     1.560039    -0.000002
H      0.892957    -3.664549     0.000043
H     -1.874998     2.507621     0.000039
C      3.487580    -2.843773    -0.000123
H      4.396833    -2.240819     0.000752
H      3.509747    -3.495577     0.878368
H      3.510557    -3.494165    -0.879649
O      0.532549     3.636362     0.000033
```

```
H     -0.304464     4.113616     0.000049
N     -2.509485    -0.100151    -0.000003
H     -2.543684    -1.106394    -0.000149
C     -3.736956     0.526242     0.000013
O     -3.875568     1.738985     0.000135
C     -4.901187    -0.432898    -0.000200
H     -4.874108    -1.075693    -0.883770
H     -4.873456    -1.077069     0.882340
H     -5.826577     0.138642     0.000561
```

3.4.14 T2(a)

```
E = -724.3674364 Hartree
Zero-point correction = 0.224368 Hartree
Thermal correction to Energy = 0.238902 Hartree
Thermal correction to Gibbs Free Energy = 0.181262 Hartree

Coordinates (Å):
C     -3.242272    -0.841418    -0.000024
C     -2.768037     0.452280     0.000025
C     -1.384526     0.743687     0.000027
C     -0.449479    -0.329748    -0.000016
C     -0.952149    -1.651682    -0.000088
C     -2.303579    -1.900066    -0.000094
H     -3.451496     1.295124     0.000046
C      0.947562     0.016084    -0.000024
H     -0.285033    -2.507373    -0.000188
C      1.302100     1.346283    -0.000033
C      0.269350     2.309198     0.000016
N     -1.013900     2.055365     0.000052
H     -2.658353    -2.925563    -0.000172
H      2.335500     1.652213    -0.000056
C     -4.713740    -1.141181     0.000065
H     -5.307901    -0.226150    -0.000935
H     -4.993551    -1.730244    -0.878435
H     -4.993787    -1.728414     0.879724
O      0.658341     3.597306     0.000010
H     -0.149985     4.128979     0.000041
N      1.880035    -1.012316    -0.000061
H      1.507969    -1.947696     0.000138
C      3.255972    -0.931237    -0.000027
O      3.870460     0.122972    -0.000098
C      3.936248    -2.278030     0.000157
H      3.653169    -2.855812     0.883744
H      3.652042    -2.856747    -0.882452
```

H 5.013359 -2.126905 -0.000593

4 Wiberg Bond Indices

Figures S7–S10 display the Wiberg bond indices for the key bonds in T1 and T2 of both systems (4-amino and 4-acetamido), in gas phase and DMSO. The indices are shown directly on the molecular structures. Some numerical values are summarised in Table S7.

4.1 4-Amino

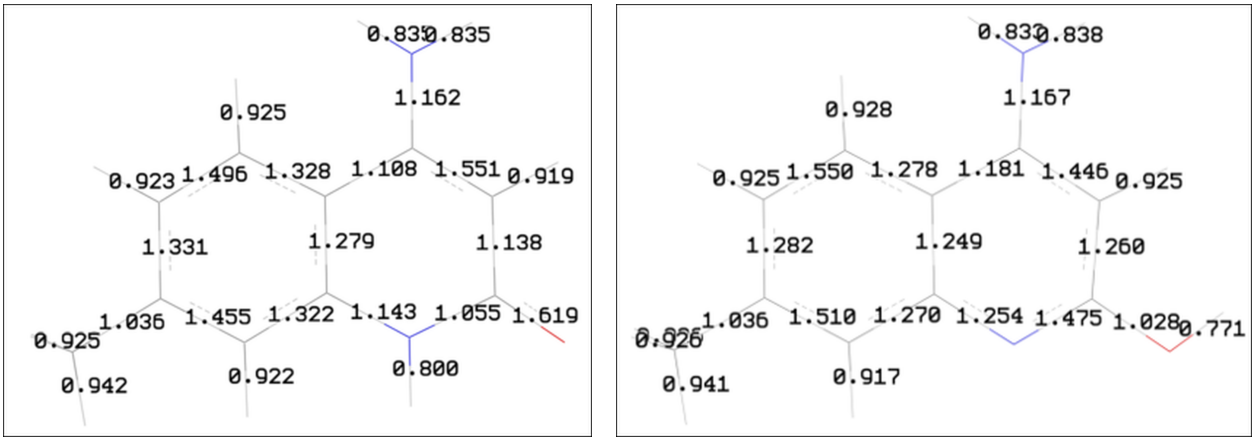

Figure S7: Wiberg bond indices for the 4-amino system in gas phase: T1 (left) and T2 (right).

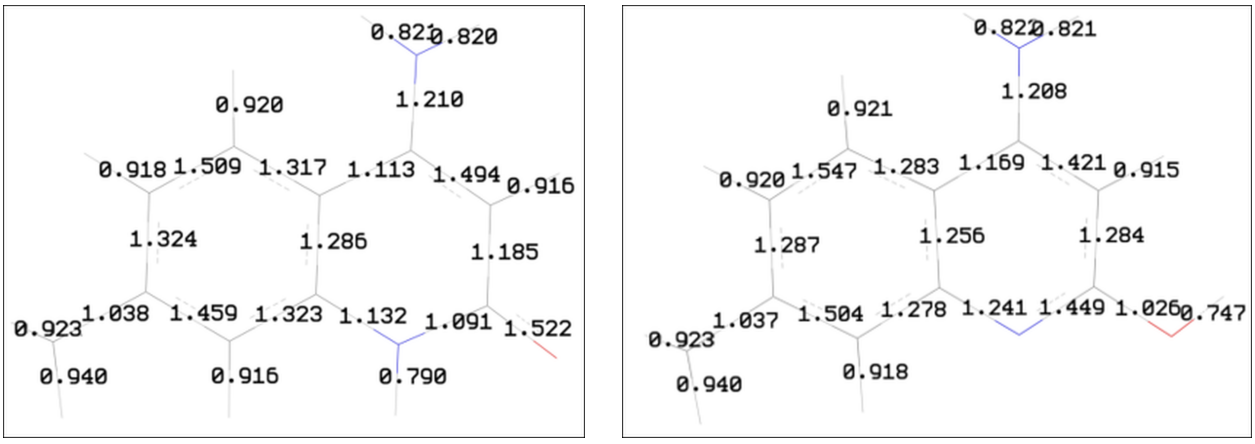

Figure S8: Wiberg bond indices for the 4-amino system in DMSO.

4.2 4-Acetamido

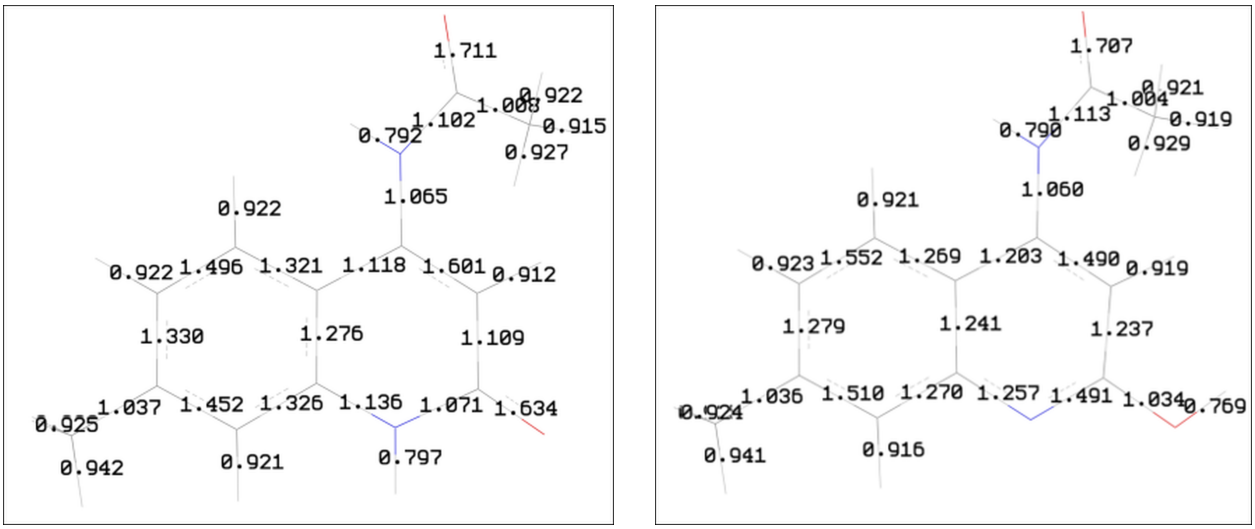

Figure S9: Wiberg bond indices for the 4-acetamido system (M1) in gas phase.

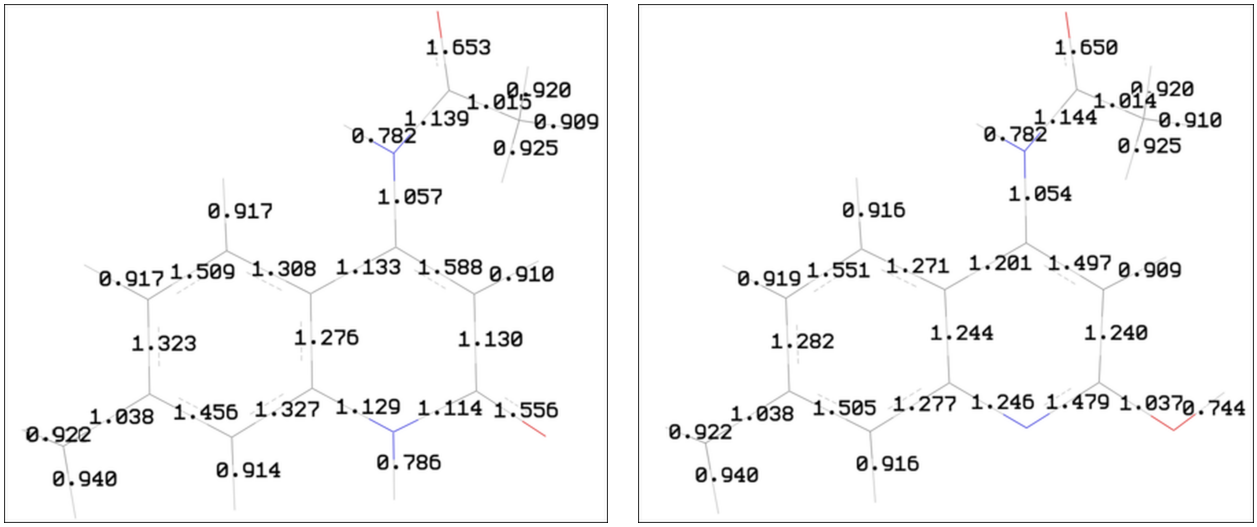

Figure S10: Wiberg bond indices for the 4-acetamido system (M1) in DMSO.

Table S7: Wiberg bond indices (WBIs) for selected bonds.

System	Solvent	Bond	T1	T2
4-Amino	Gas	C2–O	1.619	1.028
		N1–C2	1.055	1.475
		C4–N	1.162	1.167
	DMSO	C2–O	1.522	1.026
		N1–C2	1.091	1.449
		C4–N	1.210	1.208
4-Acetamido (M1)	Gas	C2–O	1.634	1.034
		N1–C2	1.071	1.491
		C4–N	1.065	1.060
	DMSO	C2–O	1.556	1.037
		N1–C2	1.114	1.479
		C4–N	1.057	1.054