A Thermochemical Computational Study on Hydroxyquinolines and their Azulene Analogues

Moyassar M. Meshhal, Safinaz H. El-Demerdash, Ahmed M. El-Nahas*
Chemistry Department, Faculty of Science, Menoufia University, 32512 Shebin El-Kom, Egypt.

Abstract

Ab initio CBS-QB3 method has been used to determine gas-phase enthalpies of formation for 34 compounds including a number of hydroxyquinoline isomers, the corresponding azulene analogues and their parent systems. The mean absolute deviation of 4.43 kJ/mol reveals good agreement between our results and the available experimental data. Relative thermodynamic stabilities of hydroxyquinoline isomers and related analogues were discussed and several isomerization reactions enthalpies were derived. The same level of theory has also been utilized to calculate adiabatic ionization energies and electron affinities for the molecules with known experimental values and the agreement between theory and experiment was found to be within 8 kJ/mol.

Keyword: Enthalpy of formation, ionization energy, quinoline, hydroxyquinoline, azulenes, CBS-QB3.

Corresponding author
Email: amelnahas@hotmail.com (Ahmed M. El-Nahas)
Tel: 002-01064607974

1. Introduction

Nitrogen-containing heterocyclic compounds are very important as they play vital roles in plenty of biologically active natural products. Quinoline and its derivatives represent a class of these compounds which have diverse pharmacological and biological activities such as anticancer [1], antibacterial [2], anticonvulsant [3], anti-inflammatory [4] and antimalarial activities [5]. In addition, they have also been reported as treatments for Alzheimer's disease [6] and rheumatoid arthritis [7].

Azulene is a fully conjugated and stable organic molecule consists of two fused rings; one is a seven-membered ring, while the other is a five-membered one. It has biological activities against ulcer, bacterial [8,9] and mucous diseases [10]. Moreover, due to its antioxidant activity, it prevents skin defects and saves skin cells from deterioration that causes wrinkles [11,12]. Therefore, azulene is a common ingredient in many cosmetics and body care products.

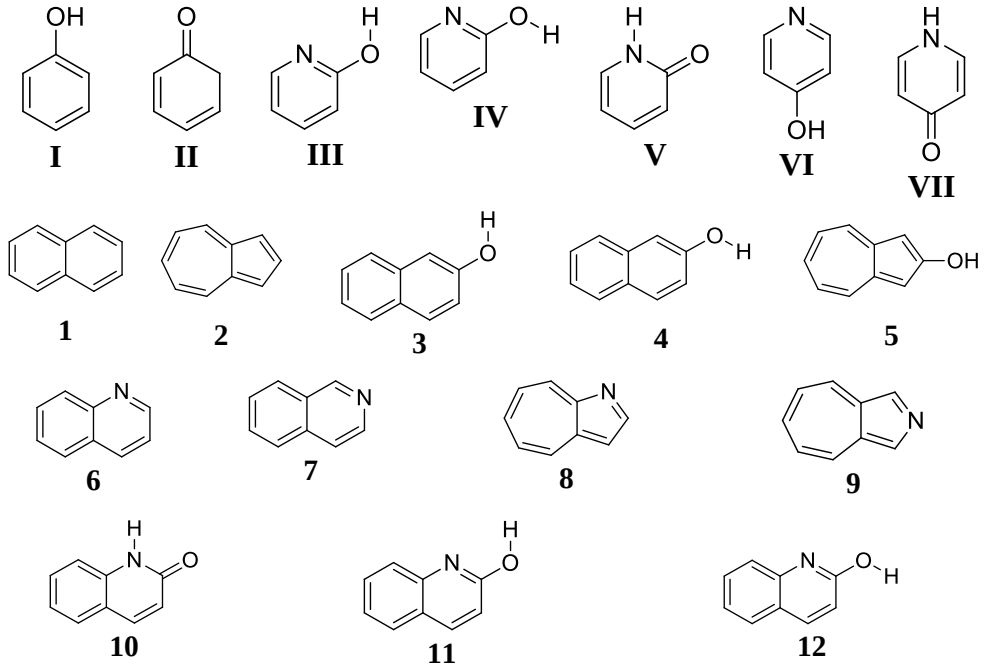
There is no doubt that reliable and wide databases of thermodynamic and kinetic parameters (e.g. standard molar enthalpies of formation, bond dissociation enthalpies, activation energies, ionization energies, electron affinities, etc.) are essentially required for understanding chemical problems, such as energetic of the chemical bonds, structural properties and reactivity, in addition to many applied areas like chemical industry, biochemistry, medical and life sciences, environmental chemistry and military matters. Nevertheless, there is a huge disparity between the extent of the experimental thermochemical databases and the number of known molecules. This gap becomes wider every day because of the increasing number of newly-prepared molecules with difficulty of measuring thermochemical properties for all the known compounds.

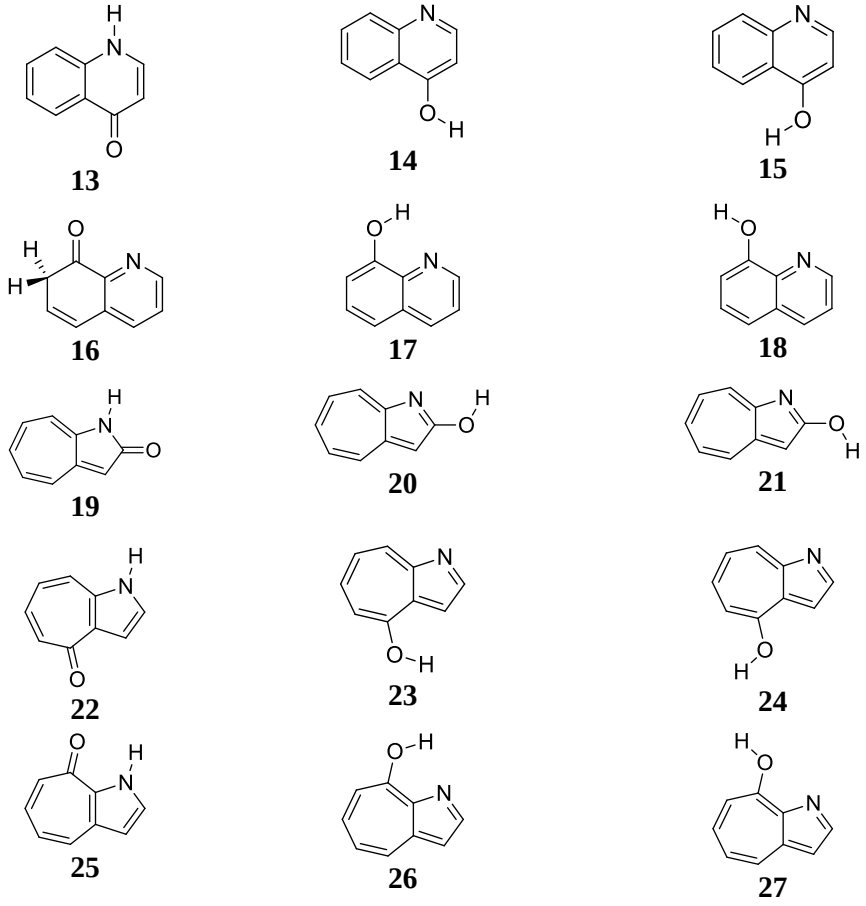
In other words, the experimental thermochemical data with high accuracy [13] are available only for a little number and certain classes of compounds. For example, the availability of experimental gas-phase molar enthalpies of formation for a large number of benzene derivatives allowed Cox [14] to develop a method to estimate enthalpies of formation of this class of compounds based on constant increment of the enthalpy of formation by the substitution of a particular group regardless of its position. On contrary, estimating enthalpies of formation for heterocyclic compounds is much more difficult and problematic because of not only the lack of such prediction schemes but also the rareness of the experimental thermochemical data for the main compounds of this family.

Accurate thermochemical data for organic compounds containing C, H, N and O atoms are required to support kinetic simulation and modeling of the reactions of these species in different environments. Because of the shortage of the experimental data, quantum chemistry has been involved to fill this breach and to examine the accuracy of the experimental methods. The good agreement between the computational enthalpies of formation and the experimentally available ones gives confidence on the unknown experimental values for other species.

The experimental gas-phase enthalpies of formation of hydroxyquinolines (e.g. 2-hydroxyquinoline, 4-hydroxyquinoline and 8-hydroxyquinoline) have been derived from the measurements of combustion enthalpies obtained by static bomb calorimetry [15–17]. Theoretical estimations have also been done for enthalpies of formation of 2-hydroxyquinoline and some hydroxy iso-quinolines employing high-level composite methods such as G3(MP2), G3(MP2)//B3LYP and G3//B3LYP [18].

The current study determines gas-phase enthalpies of formation for a number of hydroxyquinolines and their keto-tautomers (compounds **10**-**18**) as well as the corresponding aza-azulene analogues (compounds **19**-**27**). Moreover, parents of these species (compounds **1**-**9**) also have been investigated. All structures are presented in Scheme 1. Furthermore, ionization energies and electron affinities of these systems have also been estimated. The ab initio composite CBS-QB3 method has been used for this purpose.





Scheme 1. The species studied in the present work.

2. Computational methods

Geometry optimizations, frequency, and single point energy calculations were carried out using ab initio CBS-QB3 model chemistry [19] which includes the hybrid density functional theory (DFT) of Becke's three-parameter (B3) exchange-Lee, Yang, and Parr (LYP) correlation functional (B3LYP) [20–22] in conjunction with the 6-311G(d,p) basis set [23] and ends with CCSD(T) to get basis set extrapolations limit. This method has been selected for the current study because of its high-accuracy performance in addition to its relatively low computational cost relative to other sophisticated methods. Moreover, previous studies have demonstrated that the CBS-QB3 is comparable in accuracy to G3 models [19,24,25] and the average systematic error for this approach in formation enthalpy calculations is 1.2 kcal/mol (5.0 kJ/mol) [24]. Ab initio molecular orbital computations have been performed using the Gaussian 09 suit [26]. Frequency calculations have been conducted to characterize minima and transitions states from the positive and one negative frequencies, respectively, and to correct energies for zero-point energy and thermal contributions.

The standard gas-phase enthalpies of formation of the considered compounds have been obtained through following the atomization procedure described by Ochterski [27]. This methodology includes, at first, the calculation of the enthalpy of formation of a molecule at 0 K ($\Delta_f H°_{0K}$) by subtracting the computational atomization energy of the compound from the sum of the experimental enthalpies of formations of its elements ($\Delta_f H^{exp}_{0K}$) in their atomic state (given in Table S1 in the supporting information) as the following equation:

$$\Delta_f H°_{0K} = \sum \Delta_f H^{exp}_{0K} - \left[\sum E^{comp}_{0K}(elements) - E^{comp}_{0K}(molecule) \right] \quad \text{(eq. 1)}$$

where E^{comp}_{0K} is computed zero-point energy. Then, the enthalpy of formation at 298 K ($\Delta_f H°_{298K}$) can be estimated using equation (eq. 2):

$$\Delta_f H°_{298K} = \Delta_f H°_{0K} + \Delta H_{298-0}(molecule) - \sum \Delta H_{298-0}(elements) \quad \text{(eq. 2)}$$

where ΔH_{298-0} refers to the thermal corrections.

3. Results and discussion

3.1. Enthalpies of Formation

The computationally estimated enthalpies of formation versus the corresponding experimental ones are displayed in Table 1. As can be seen in Table 1, the calculated enthalpies of formation of compounds **I** (phenol), **III** (2-hydroxypyrridine) and **VI** (4-hydroxypyrridine) are in good agreement with their relevant experimental data (for **I** cf. reference [28], while for **III** and **VI** cf. reference [29]) with deviations of 3.1 kJ/mol, -5.26 kJ/mol and 3.34 kJ/mol, respectively. For naphthalene (**1**), seven values have been reported in the NIST WebBook [30] as its experimental enthalpy of formation in the gas-phase. The average of these values, 150 ±1 kJ/mol as shown in Table 1, is lower than our computed value by 5.9 kJ/mol.

The gas-phase enthalpy of formation of azulene (**2**) has been determined experimentally by Kovats et al. [30], Roth et al. [31] and Sousa et al. [32] to be 280.0, 308.0 and 288.1 ±5.3 kJ/mol, respectively. On the other hand, it has been estimated theoretically by Sousa and co-workers to be 295.0 and 299.0 kJ/mol, according to the G3 and G4 methods, respectively. Quite good agreement, within 2.0 kJ/mol, has been observed between the value calculated at the G4 level of theory, by Sousa et. al., and the value estimated at CBS-QB3. Moreover, the relative stability of naphthalene over azulene has been calculated by the same group, Sousa et. al., [32] (at the theoretical levels G3 and G4) to be 147.9 kJ/mol comparing very well with our prediction (145.1 kJ/mol).

Table 1. The standard gas-phase molar enthalpies of formation $\Delta_f H°_{298K}$ calculated at the CBS-QB3 method vs. the available experimental ones, and the differences between the experimental and calculated results $\Delta\Delta_f H°_{exp-comp}$ (kJ/mol).

Species	$\Delta_f H°_{298K}$		$\Delta\Delta_f H°_{exp-comp}$
	comp.	***exp.***	
I	-91.10	-94.2	3.1
II	-10.56		
III	-74.44	-79.7 ± 1.5	-5.26
IV	-53.71		
V	-68.59		
VI	-44.14	-40.8 ± 2.1	3.34
VII	-28.82		
1	155.90	150.0 ±10	-5.90
2	301.04	307.5	6.46
3	-25.77	-29.9 ±1.7	-4.13
4	-23.79		
5	115.28		
6	204.16	200.5	-3.66
7	208.77	204.61	-4.16
8	322.40		
9	354.31		
10	-28.70		
11	-17.80	-25.5 ±2.4	-7.7
12	4.60		
13	10.48		
14	16.23	20.8 ±2.3	4.57
15	19.53		
16	84.43		
17	1.94	6.5 ±1.7	4.56
18	34.36		
19	88.34		
20	106.70		
21	123.15		
22	93.82		
23	126.85		
24	132.18		
25	74.85		
26	101.98		
27	145.63		

The enthalpies of formation of quinoline (**6**) and isoquinoline (**7**) have been estimated both experimentally and theoretically. The experimental estimates [30] have

been found in between our results and the G3//B3LYP value by Namazian and Coote [18]. The CBS-QB3 method overestimates the experimental measurements by 3.7 kJ/mol for **6** and 4.2 kJ/mol for **7**, while the G3//B3LYP results underestimate them by 2.9 and 2.3 kJ/mol, respectively.

The experimental enthalpies of formation of 2-hydroxyquinoline (**11** or **12**), 4-hydroxyquinoline (**14** or **15**), and 8-hydroxyquinoline (**17** or **18**) have been reported [15–17]. For 2-hydroxyquinoline, da Silva et al. [15] reported –25.5 ±2.4 kJ/mol which underestimates our result for conformer **11** (–17.8 kJ/mol) by 7.7 kJ/mol. Taking into account the systematic error of the CBS-QB3 method and the uncertainty of the experimental value indicates good agreement between the experimental and theoretical findings. Furthermore, Namazian and Coote [18] estimated – 22.7 kJ/mol for the enthalpy of formation of 2-hydroxyquinoline at the G3//B3LYP level of theory which lies between our value and the experimental one showing good agreement with both of them. In an attempt to reproduce their work, when applying the same level of theory (G3//B3LYP) and procedure (following the reference they mentioned) we obtained –33.5 kJ/mol which is far from the result they reported. We found that the source of this deviation is the experimental value of the enthalpy of formation of gaseous hydrogen atom at 0 K used in the calculations. In other words, according to Nicolaides et al. [33] (the reference they cited) as well as our calculations this value is 51.6 kcal/mol (≈ 216.0 kJ/mol), while approximating this value to 52.0 kcal/mol reproduces the exact value of enthalpy of formation of 2-hydroxyquinoline reported by Namazian and Coote [18].

The experimental gas-phase enthalpy of formation for 4-hydroxyquinoline of 20.8 ±2.3 kJ/mol has been reported by da Silva and co-workers [15]. Apparently, there are two rotamers of 4-hydroxyquinoline (**14** and **15**) due to the rotation of the OH group. The computational enthalpies of formation for these two conformers (16.2 and 19.5 kJ/mol, respectively) show good agreement with the reported experimental gas-phase enthalpy of formation of 4-hydroxyquinoline. The difference in free energies (ΔG_{289}) between **14** and **15** has been found to be 1.7 kJ/mol and the equilibrium constant for the rotamerization of **14** to **1**5 has been calculated to be 0.496. Moreover, free energy of activation ($\Delta G^{\#}_{289}$) of 15.8 kJ/mol for the interconversion of **14** to **15**, shown in Fig. 1, has also been obtained through the CBS-QB3 level of theory. Therefore, such low

barrier height and slight free energy difference could suggest the presence of a dynamic equilibrium between these two conformers.

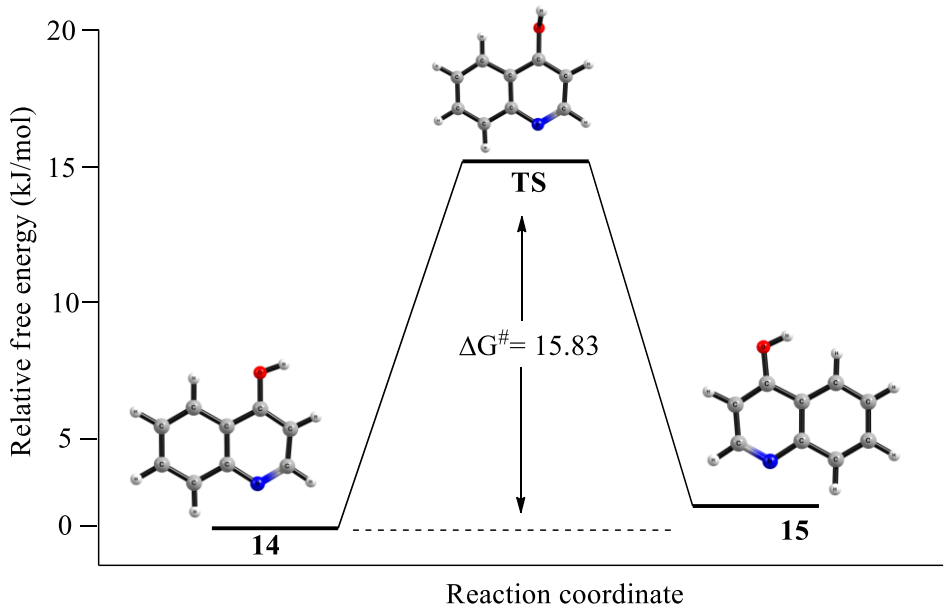


Figure 1. Free energy (in kJ/mol) diagram for the interconversion between compounds **14** and **15** calculated at CBS-QB3.

The gas-phase enthalpy of formation of 8-hydroxyquinoline of 6.5 ±1.7 and 27.6 ±2.6 kJ/mol has been estimated by da Silva et al. [16] and Sakiyama et al. [17], respectively. However, they reported quite close values for its crystalline enthalpy of formation, -83.0 ±1.5 and -81.2 ±2.0 kJ/mol, respectively. The significant discrepancy between their measurements for the gas-phase formation enthalpy arises from the different values of enthalpy of sublimation which they used to drive the gaseous molar enthalpy of formation of 8-hydroxyquinoline, since da Silva et. al. determined the enthalpy of sublimation of 8-hydroxyquinoline according to the Knudsen method (89.5 ±0.9 kJ/mol) [16], while Sakiyama et al. used the value determined by Horton and Wendlandt (108.8 ±1.7 kJ/mol) [34]. Such cases of discrepancy between experimental results raise the critical need for theoretical approaches to examine and support experiments via delivering accurate thermochemical data. Scheme 1 displays two conformers of 8-hydroxyquinoline (**17** and **18**) and defining the most stable one is needed to assign the experimental enthalpy of formation, unless there is a dynamic equilibrium between the two conformers. The equilibrium constant for **17** versus **18** has been obtained as 3.573×10^{-06} illustrating that the equilibrium is significantly shifted toward the formation of **17**. The free energy of activation for the interconversion between **17** and **18** has been calculated CBS-QB3. As given in Fig. 2, barrier heights of 41.8 and 10.7 kJ/mol for the forward and backward reactions, respectively, emphasize

the kinetic and thermodynamic stability of the conformer **17** and its predominance over **18**, as well as the absence of equilibrium at normal experimental conditions of room temperature and atmospheric pressure. Therefore, the experimental enthalpy of formation of 8-hydroxyquinoline has to be compared only with the computational enthalpy of formation of **17**. Clearly, our CBS-QB3 calculated value for **17** (1.9 kJ/mol) shows good agreement with the one reported by da Silva et al. (6.5 ±1.7 kJ/mol) with absolute deviation of 4.6 kJ/mol.

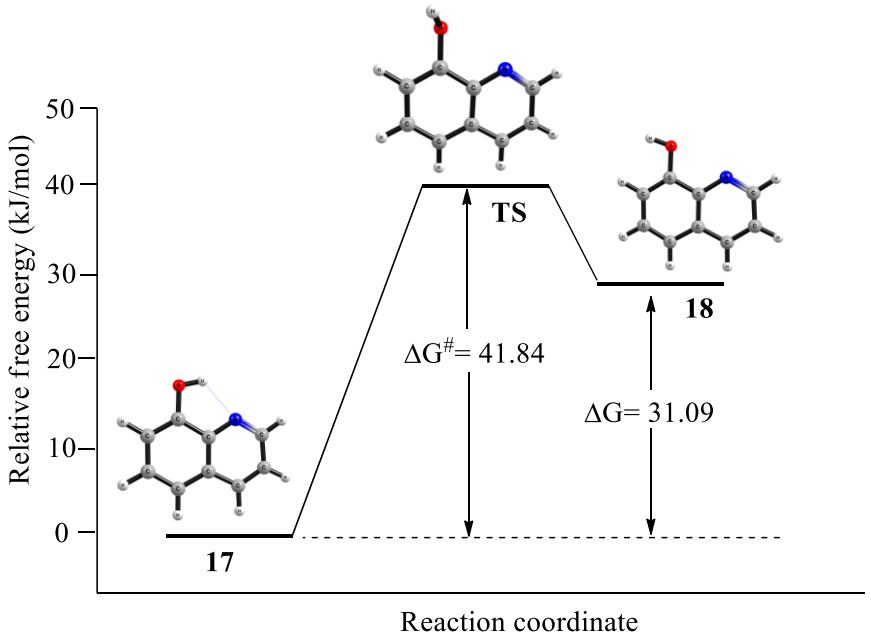


Figure 2. Free energy of activation $\Delta G^{\#}$ and relative free energy ΔG (in kJ/mol) diagram for the interconversion from **17** to **18** calculated at CBS-QB3.

From a statistical point of view, a very good correlation (y = 1.006 x - 1.7218 and R= 0.9993) has been found between the computational enthalpies of formation and the available experimental ones as illustrated in Fig 3. The mean absolute deviation from experiment has been found to be 4.43 kJ/mol, within the typical demonstrated error for the CBS-QB3 method (≈ 5.0 kJ/mol) [24]. Such good agreement between the computational and experimental data validates the use of the CBS-QB3 approach for estimating accurate enthalpies of formation for the selected molecules and other related chemical systems.

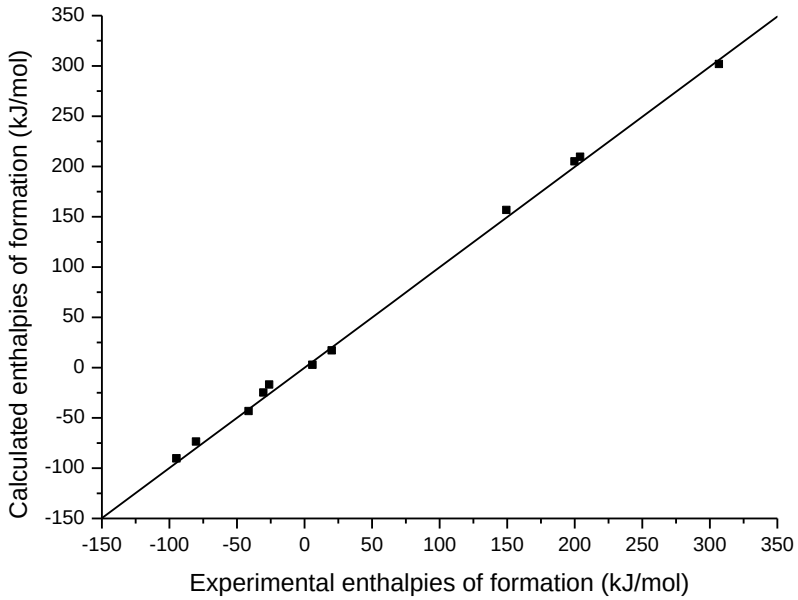
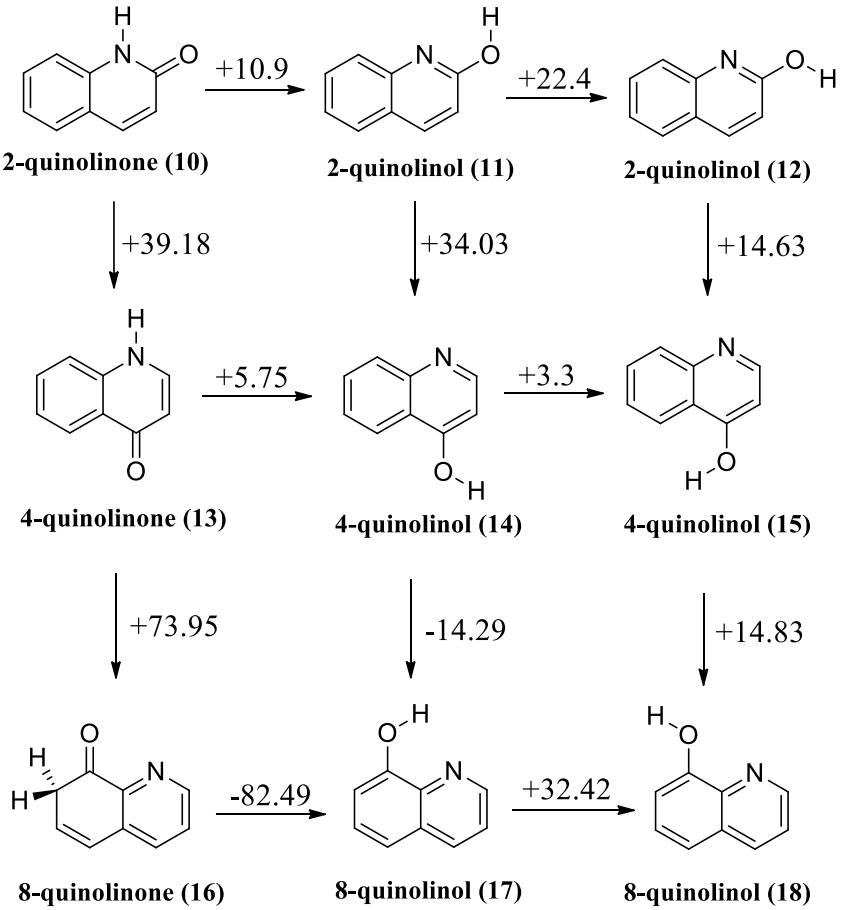


Figure 3. CBS-QB3 vs. Experimental enthalpies of formation.

The relative thermodynamic stability of the investigated systems can be discussed in the light of their enthalpies of formation. An insight into Table 1 and Scheme 2 indicates that introducing the OH group in position 2 gives the most stable hydroxyquinoline isomer (**11**) followed by position 8 (isomer **17**) with isomerization enthalpy 19.7 kJ/mol. However, as can be seen in Table 1 and Scheme 3, a different stability trend has been observed in the corresponding hydroxy aza-azulene analogues where the presence of the OH group in position 8 (**28**) reveals slightly more stability than in position 2 (**20**) with isomerization enthalpy of 4.7 kJ/mol.

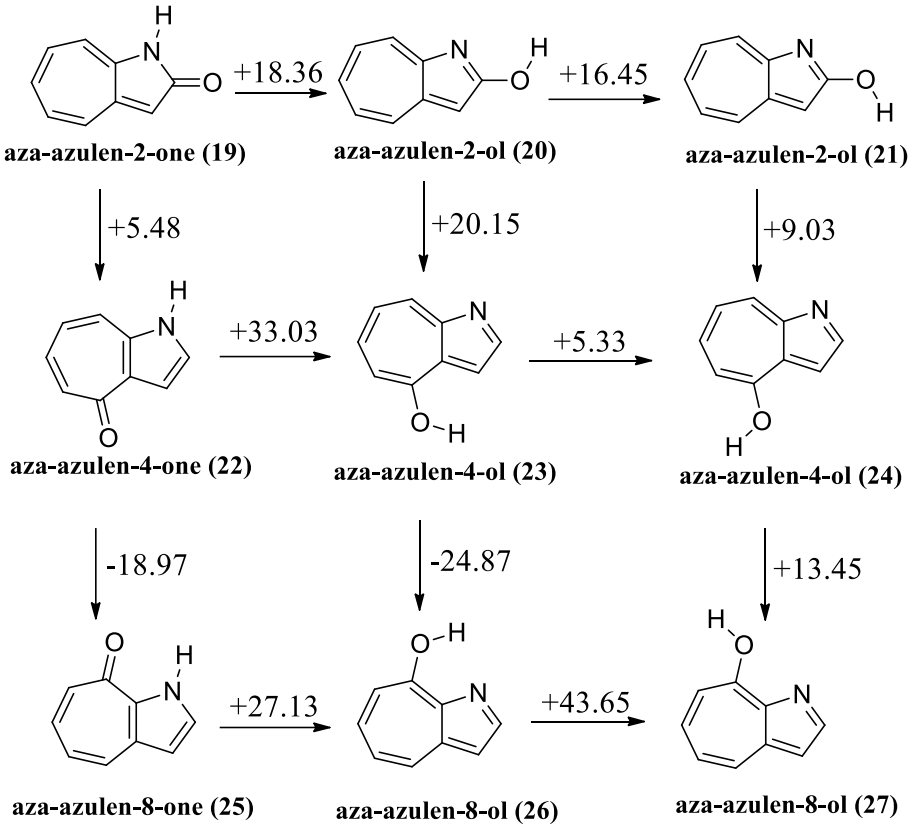
The stability of keto and enol tautomers depends on many factors such as the formed and broken bond strength, presence or absence of hydrogen bond, steric effect, solvent and polarity of each form, aromaticity and conjugation. In contrast to hydroxyquinolines and according to the position of the carbonyl group, the stability order in quinolinones shows that position 4 exhibits more stability than position 8, while position 2 remains the most stable. The higher stability of 2-quinolinone (**10**) arises mainly from the strength of the C=O relative to the C=C bond because comparable intramolecular hydrogen bonds exist in some in **10**, **11**, and **17**. Compared to hydroxyquinolines and quinolinones, all keto forms of the azulene analogues are more stable than their enols and the keto form at position 8 (**25**) appears as the most stable one due to the difference in the strength of C=O and C=C bonds among tautomers/rotomers and existence of intramolecular hydrogen bond that is a part of five-

membered ring. Other forms (**19**, **20**, **22**, and **26**) lack either no C=O, four-membered ring or no hydrogen bond.



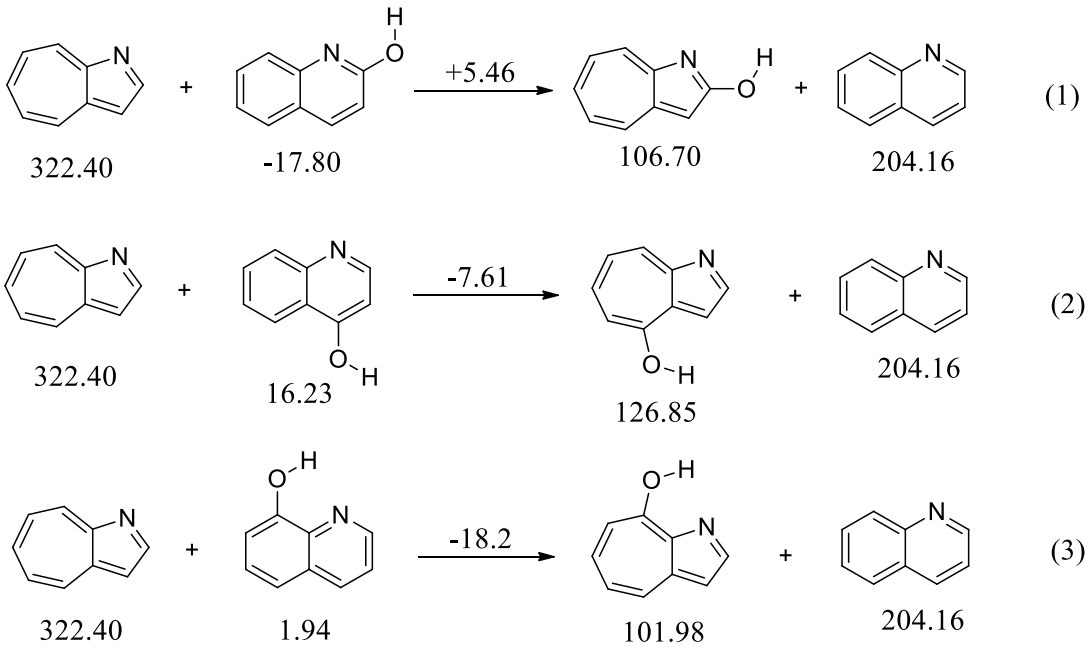
Scheme 2. CBS-QB3 enthalpies of isomerisation and keto-enol tautomerization reactions ($\Delta\Delta_fH_{298}$, kJ/mol) between compounds **10**-**18**.

The positive ΔH values of all enolization reactions, except in case of 8-quinolinone, reveal the higher stability of the keto tautomers relative to their corresponding enols. More values for the enthalpies of isomerization and keto-enol tautomerization reactions are displayed in Schemes 2 and 3.



Scheme 3. CBS-QB3 enthalpies of isomerisation and keto-enol tautomerization reactions ($\Delta\Delta_fH_{298}$, kJ/mol) between compounds **19**-**27**.

Comparing enthalpies of formation of hydroxyquinolines with that of the corresponding azulene analogues and their parent compounds (quinoline **6** and aza-azulene **8**, respectively) reveals that the introduction of the OH group on the parent systems stabilizes these chemical species. The degree of stability varies depending on the parent skeleton as well as on the position of the OH group. The differences in the stabilization energies accompanying the insertion of OH group can be discussed via the hypothetical reactions presented in Scheme 4. The positive ΔH value of reaction (1) reflects the higher thermodynamic stabilizing effect of the OH group in quinoline in position 2 relative to aza-azulene at the same position. It also confirms the higher stability of **11** compared to other hydroxyquinoline isomers. On the other hand, the negative ΔH values of reactions (2) and (3) show that inserting the OH group into positions 4 and 8 in aza-azulene is accompanied by more stabilization when compared with quinoline. In addition, the more negative ΔH value of reaction (3) indicates the higher thermodynamic stability of **26** over the remaining hydroxy aza-azulene isomers.



Scheme 4. CBS-QB3 enthalpies ($\Delta\Delta_rH_{298}$, kJ/mol) of hypothetical reactions for introduction of OH group into positions 2, 4 and 8 in quinoline and the corresponding aza-azulene analogues. The value shown below each molecule represents its computed enthalpy of formation (in kJ/mol).

3.2. Ionization Energies and Electron Affinities

Ionization energy (IE) and electron affinity (EA) are important terms for understanding and determining many molecular reactivity descriptors such as hardness, softness, electronegativity, chemical potential and the electrophilicity index [35,36]. The ionization energy is the minimum energy required to release an electron from a neutral atom or molecule in its ground state to give a cation. It can be calculated by subtracting the energy of the neutral compound from the energy of the formed molecular cation (cf. eq. 3).

$$IE = E(N^+) - E(N) \qquad \text{(eq. 3)}$$

Where $E(N^+)$ is the energy of the molecular cation and E(N) is the energy of the neutral molecule. Considering in calculations the process of geometrical rearrangement taking place in the molecular cation after the electron ejection yields the adiabatic ionization energy (AIE), whereas the vertical ionization energy (VIE) is obtained when considering the energy of the molecular cation with the same geometry of the neutral molecule [35,36]. On the other hand, the electron affinity is defined as the amount of energy released when an electron is gained by a neutral atom or molecule [36]. It is calculated by subtracting the energy of the molecular anion from the neutral molecule's energy (cf. eq. 4).

$$EA = E(N) - E(N^-) \qquad \text{(eq. 4)}$$

Where $E(N^-)$ is the energy of the molecular anion. Similar to ionization energy, there are two types of electron affinities; adiabatic electron affinity (AEA) and vertical electron affinity (VEA). Electron affinities may be either positive or negative. The positive EA means that the incoming electron is bound, while the negative value means that the added electron is unbound [36].

AIEs and AEAs of selected molecules, with available experimental data, have been estimated theoretically using CBS-QB3, and the results versus their corresponding experimental data are presented in Table 2. The AEAs of **1** and **2** were determined experimentally by Schiedt et. al. [37] to be -19.30 and 76.22 kJ/mol, respectively, which are in good agreement with the values reported by ourselves -12.54 and 72.36 kJ/mol , respectively. Likewise, the AIE estimations presented here reveal quite good agreement with their corresponding experimental ones with mean absolute deviation of 8 kJ/mol.

Koopmans' theorem offers an alternative approach to estimate IE and EA directly from the energies of the HOMO and LUMO, respectively [36]. According to this approach, the ionization energy for a molecule is the negative of its HOMO's energy, while its electron affinity is the negative of its LUMO's energy. Apparently, the IEs and EAs obtained according to Koopmans' theorem cannot be considered the adiabatic ones, since no geometrical rearrangement is taken into account.

Table 2. The computational vs. experimental adiabatic ionization energies (AIEs) and adiabatic electron affinities (AEAs), in kJ/mol, for the systems with available experimental data.

Systems	**AIEs**			**AEAs**	
	Comp.	**Exp.**	**Δ IEs**[a]	**Comp.**	**Exp.**
1	788.28	785.39[b]	2.89	-12.54	-19.30
2	724.60	715.92[b]	8.68	72.36	76.22
3	768.99	759.34[c]	9.65		
6	837.49	832.67[d]	4.82		
7	829.77	823.02[e]	6.75		
10	790.21	810.47[f]	-20.26		
11	812.40	810.47[f]	1.93		
13	783.46	791.18[f]	-7.72		
14	813.37	791.18[f]	22.19		

[a] Δ **IE** = $\mathbf{AIE_{(Comp.)}}$ - $\mathbf{AIE_{(Exp.)}}$

[b] Ref. [39]

[c] Ref. [40]

[d] Ref. [41]

[e] Ref. [42]

[f] Ref. [43]

In the context of the ab initio methods, Koopmans' theorem gives very good estimates for the ionization energy but not for the electron affinities [36,38]. However, it may be useful in describing trends of reactivity descriptors in a class of compounds. Table S2 presents the ionization energies and electron affinities for the investigated 27 species based on Koopmans' theorem where the energies of HOMOs and LUMOs were extracted from the MP4SDQ/CBSB4 calculations as given in the CBS-QB3 method.

Conclusions

Accurate estimates of enthalpies of formation have been obtained using the CBS-QB3 model chemistry for a series of aromatic and heteroaromatic compounds including naphthalene, azulene, 2-naphthol, 2-hydroxyazulene, number of hydroxyquinoline isomers and their azulene analogues. The very good agreement found between theory and experiment (within 4.43 kJ/mol) validates the CBS-QB3 method for benchmarking heats of formation for this family of compounds. Relative thermodynamic stabilities of the hydroxyquinoline tautomers and their azulene analogues have been discussed depending on their enthalpies of formation. Enthalpy changes for several isomerization reactions have also been calculated from the computed enthalpies of formation. Moreover, the adiabatic ionization energies and electron affinities of selected systems have been estimated at the same level of theory. Similar to enthalpies of formation, our calculations agree well with experimental ionization energies with mean absolute deviation of 8 kJ/mol.

References

[1] M. Chen, H. Chen, J. Ma, X. Liu, S. Zhang, Synthesis and anticancer activity of novel quinoline-docetaxel analogues, Bioorg. Med. Chem. Lett. 24 (2014) Bioorg. Med. Chem. Lett. doi:https://doi.org/10.1016/j.bmcl.2014.04.091.

[2] N. Nayak, J. Ramprasad, U. Dalimba, Synthesis and antitubercular and antibacterial activity of some active fluorine containing quinoline-pyrazole hybrid derivatives, J. Fluor. Chem. 183 (2016) 59–68. doi:http://dx.doi.org/doi:10.1016/j.jfluchem.2016.01.011.

[3] L.J. Guo, C.X. Wei, J.H. Jia, L.M. Zhao, Z.S. Quan, Design and synthesis of 5-alkoxy-[1,2,4]triazolo[4,3-a]quinoline derivatives with anticonvulsant activity, Eur. J. Med. Chem. 44 (2009) 954–958. doi:10.1016/j.ejmech.2008.07.010.

[4] M. Pinz, A.S. Reis, V. Duarte, M.J. Da Rocha, B.S. Goldani, D. Alves, L. Savegnago, C. Luchese, E.A. Wilhelm, 4-Phenylselenyl-7-chloroquinoline, a new quinoline derivative containing selenium, has potential antinociceptive and anti-inflammatory actions, Eur. J. Pharmacol. 780 (2016) 122–128. doi:10.1016/j.ejphar.2016.03.039.

[5] S. Vandekerckhove, M. D'Hooghe, Quinoline-based antimalarial hybrid compounds, Bioorganic Med. Chem. 23 (2015) 5098–5119. doi:10.1016/j.bmc.2014.12.018.

[6] J. Fiorito, F. Saeed, H. Zhang, A. Staniszewski, Y. Feng, Y.I. Francis, S. Rao, D.M. Thakkar, S.X. Deng, D.W. Landry, O. Arancio, Synthesis of quinoline derivatives: Discovery of a potent and selective phosphodiesterase 5 inhibitor for the treatment of Alzheimer's disease, Eur. J. Med. Chem. 60 (2013) 285–294. doi:10.1016/j.ejmech.2012.12.009.

[7] Y. Hu, N. Green, L.K. Gavrin, K. Janz, N. Kaila, H.Q. Li, J.R. Thomason, J.W. Cuozzo, J.P. Hall, S. Hsu, C. Nickerson-Nutter, J.B. Telliez, L.L. Lin, S. Tam, Inhibition of Tpl2 kinase and TNFα production with quinoline-3-carbonitriles for the treatment of rheumatoid arthritis, Bioorganic Med. Chem. Lett. 16 (2006) 6067–6072. doi:10.1016/j.bmcl.2006.08.102.

[8] J. Frigola, J. Pares, J. Corbera, V. David, R. Merce, A. Torrens, J. Mas, E. Valenti, 7-Azetidinylquinolones as Antibacterial Agents. Synthesis and Structure-Activity Relationships, J. Med. Chem. 36 (1993) 801–810.

[9] S. Wakabayashi, H. Sekiguchi, K. Kosakai, S. Mochizuki, M. Kashima, A. Tomiyama, General pharmacological properties of an anti-ulcer drug, azuletil sodium (KT1-32), Folia Pharmacol. Jpn. 96 (1990) 185–204.

[10] R. Hamajima, T. Fujimoto, H. Okuda, Studies on azulene derivatives (Ⅱ). Absorption, distribution, metabolism and excretion of sodium guaiazulene-3-sulfonate, Appl. Pharmacol. 12 (1976) 501–510.

[11] L. Wang, J. Yan, P.P. Fu, K.A. Parekh, H. Yu, Photomutagenicity of cosmetic ingredient chemicals azulene and guaiazulene, Mutat. Res. - Fundam. Mol. Mech. Mutagen. 530 (2003) 19–26. doi:10.1016/S0027-5107(03)00131-3.

[12] H.M. Chiang, J.J. Yin, Q. Xia, Y. Zhao, P.P. Fu, K.C. Wen, H. Yu, Photoirradiation of azulene and guaiazulene-Formation of reactive oxygen species and induction of lipid peroxidation, J. Photochem. Photobiol. A Chem.

211 (2010) 123–128. doi:10.1016/j.jphotochem.2010.02.007.

[13] J.D. Cox, G. Pilcher, Thermochemistry of Organic and Organo-metallic Compound, Academic Press, London and New York, 1970.

[14] J.D. Cox, A Method for Estimating the Enthalpies of Formation of Benzene Derivatives in the Gas State, NPL Rep. Chem. 83 (1978).

[15] M.A.V.R. da Silva, M.A. Matos, M.J.S. Monte, Enthalpies of combustion, vapour pressures, and enthalpies of sublimation of 5-amino-6-nitroquinoline and 4-aminoquinaldine.pdf, J. Chem. Phys. 22 (1990) 609–616.

[16] M.A.V.R. da Silva, M.J.S. Monte, M.A. Matos, Enthalpies of combustion, vapour pressures, and enthalpies of sublimation of 8-hydroxyquinoline, 5-nitro-8-hydroxyquinoline, and 2-methyl-8-hydroxyquinoline, J. Chem. Thermodyn. (1989) 159–166.

[17] M. Sakiyama, T. Nakano, S. Seki, Enthalpies of Combustion of Organic Compounds. I. 8-Quinolinol, Bullentin Chem. Soc. Japan. 48 (1975) 1708–1708.

[18] M. Namazian, M.L. Coote, Calculation of the enthalpies of formation and proton affinities of some isoquinoline derivatives, J. Chem. Thermodyn. 40 (2008) 1627–1631. doi:10.1016/j.jct.2008.07.007.

[19] J.A. Montgomery, M.J. Frisch, J.W. Ochterski, G.A. Petersson, A complete basis set model chemistry. VI. Use of density functional geometries and frequencies, J. Chem. Phys. 110 (1999) 2822–2827. doi:10.1063/1.477924.

[20] A.D. Becke, Density-Functional Thermochemistry. III. The Role of Exact Exchange, J. Chem. Phys. 98 (1993) 5648–5652. doi:10.1063/1.464913.

[21] C. Lee, W. Yang, R.G. Parr, Development of the Cille-Savetti correlation-energy formula into a functional of the electron density, Phys. Rev. B. 37 (1988) 785–789.

[22] P.J. Stephens, F.J. Devlin, C.F. Chabalowski, M.J. Frisch, Ab Initio Calculation of Vibrational Absorption and Circular Dichroism Spectra Using Density Functional Force Fields, J. Phys. Chem. 98 (1994) 11623–11627. doi:10.1021/j100096a001.

[23] P.C. Hariharan, J.A. Pople, The Influence of Polarization Functions on Molecular Orbital Hydrogenation Energies, Theor. Chim. Acta. 28 (1973) 213–222. doi:10.1007/BF00533485.

[24] L.A. Curtiss, P.C. Redfern, D.J. Fruript, Theoretical Methods for Computing

Enthalpies of Formation of Gaseous Compounds, Rev. Comput. Chem. 15 (2000) 147–211.

[25] M. das D.M.. C.R. da Silva, M.A.V.R. da Silva, V.L.S. Freitas, M.V. Roux, P. Jiménez, M. Temprado, J.Z. Dávalos, P. Cabildo, R.M. Claramunt, J. Elguero, Structural studies of cyclic ureas : 3. Enthalpy of formation of barbital, J. Chem. Thermodyn. 41 (2009) 1400–1407. doi:10.1016/j.jct.2009.06.018.

[26] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G.A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H.P. Hratchian, A.F. Izmaylov, J. Bloino, G. Zheng, J.L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J.A. Montgomery, J.E. Peralta, F. Ogliaro, M. Bearpark, J.J. Heyd, E. Brothers, K.N. Kudin, V.N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J.C. Burant, S.S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J.M. Millam, M. Klene, J.E. Knox, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, R.L. Martin, K. Morokuma, V.G. Zakrzewski, G.A. Voth, P. Salvador, J.J. Dannenberg, S. Dapprich, A.D. Daniels, Farkas, J.B. Foresman, J. V Ortiz, J. Cioslowski, D.J. Fox, Gaussian 09, Gaussian 09, Gaussian, Inc., Wallingford CT. (2009).

[27] J.W. Ochterski, D. Ph, Thermochemistry in Gaussian, Gaussian Inc Pittsburgh PA. 264 (2000) 1–19. doi:10.1016/j.ijms.2007.04.005.

[28] G.S. Parks, K.E. Manchester, L.M. Vaughan, Heats of Combustion and Formation of Some Alcohols, Phenols, and Ketones, J. Chem. Phys. 22 (1954) 2089–2090. doi:10.1063/1.1740005.

[29] S. Suradi, N. El Saiad, G. Pilcher, H.. Skinner, Enthalpies of combustion of the three hydroxy-pyridines and the four hydroxy-2-methylpyridines, J. Chem. Thermodyn. 14 (1982) 45–50. doi:10.1016/0021-9614(82)90122-7.

[30] National Institute of Standards and Technology, NIST Chemistry WebBook, SRD 69, (n.d.). http://webbook.nist.gov/chemistry.

[31] W.R. Roth, M. Bohm, H.-W. Lennartz, E. Vogel, Resonance Energy of Bridged [10IAnnulenes, Angew. Chem. Int. Ed. Engl. 22 (1983) 1007–1008.

[32] C.C.S. Sousa, M.A.R. Matos, V.M.F. Morais, Energetics and stability of azulene: From experimental thermochemistry to high-level quantum chemical

calculations, J. Chem. Thermodyn. 73 (2014) 101–109. doi:10.1016/j.jct.2013.11.008.

[33] A. Nicolaides, A. Rauk, M.N. Glukhovtsev, L. Radom, Heats of Formation from G2, G2(MP2), and G2(MP2,SVP) Total Energies, J. Phys. Chem. 2 (1996) 17460–17464.

[34] G.R. Horton, W.W. Wendlandt, The heats of dissociation of the 8-quinolinol and substituted 8-quinolinol metal chelates of uranium (VI), thorium (IV) and scandium (III), J. Inorg. Nucl. Chem. 25 (1963) 241–245. doi:https://doi.org/10.1016/0022-1902(63)80048-2.

[35] S. Rayne, K. Forest, Estimated Adiabatic Ionization Energies for Organic Compounds Using the Gaussian-4 (G4) and W1BD Theoretical Methods, J. Chem. Eng. Data. 56 (2011) 350–355.

[36] E.G. Lewars, Computational Chemistry; Introduction to the Theory and Applications of Molecular and Quantum Mechanics, Third ed., Springer, 2011. doi:10.1007/978-90-481-3862-3.

[37] J. Schiedt, W.J. Knott, K. Le Barbu, E.W. Schlag, R. Weinkauf, Microsolvation of similar-sized aromatic molecules: Photoelectron spectroscopy of bithiophene–, azulene–, and naphthalene– water anion clusters, J. Chem. Phys. 113 (2000) 9470–9478. doi:10.1063/1.1319874.

[38] J.-L. Bredas, Mind the gap!, Mater. Horiz. 1 (2014) 17–19. doi:10.1039/C3MH00098B.

[39] M.J.S. Dewar, S.D. Worley, Photoelectron Spectra of Molecules. I. Ionization Potentials of Some Organic Molecules and Their Interpretation, J. Chem. Phys. 50 (1969) 654–667. doi:10.1063/1.1671114.

[40] A. Oikawa, H. Abe, N. Mikami, M. Ito, Electronic spectra and ionization potentials of rotational isomers of several disubstituted benzenes, Chem. Phys. Lett. 116 (1985) 50–54. doi:10.1016/0009-2614(85)80123-8.

[41] W. Schäfer, A. Schweig, G. Märkl, K.-H. Heier, Zur elektronenstruktur der λ3- und λ5-phosphanaphthaline - ungewöhnlich grosse mo destabilisierungen, Tetrahedron Lett. 14 (1973) 3743–3746. doi:10.1016/S0040-4039(01)87025-8.

[42] W. Schäfer, A. Schweig, H. Vermeer, F. Bickelhaupt, H. De Graaf, On the nature of the “free electron pair” on phosphorus in aromatic phosphorus compounds: The photoelectron spectrum of 2-phosphanaphthalene, J. Electron Spectros. Relat. Phenomena. 6 (1975) 91–98. doi:10.1016/0368-

2048(75)80001-6.

[43] G. Pfister-Guillouzo, C. Guimon, J. Frank, J. Ellison, A.R. Katritzky, A photoelectron spectral study of the vapour phase tautomerism of 2- and 4-quinolone, Liebigs Ann. Der Chemie. 1981 (1981) 366–375. doi:10.1002/jlac.198119810304.