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Using Chou's 5-Step Rule to Evaluate the Stability of Tautomers: Susceptibility of 2-[(Phenylimino)-methyl] -cyclohexane-1,3-diones to Tautomerization Based on the Calculated Gibbs Free Energies

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Received: 29 November 2019; Accepted: 24 December 2019; Published: 1 January 2020

Abstract: Gibbs free energies, based on DFT (Density Functional Theory) calculations, prove that enaminone (2-(anilinemethylidene)cyclohexane-1,3-dione) and ketamine (2-[(phenylimino)-methyl]cyclohexane-1,3-dione) are the most and least stable tautomeric forms of the studied systems, respectively. ^{1}H and ^{13}C NMR spectra prove that 2-(anilinemethylidene)cyclohexane-1,3-diones are the only tautomeric species present in dimethylsulfoxide solution (a very weak signal can be seen only for the p-methoxy derivatives). The zwitterionic character of these enaminones is strengthened by naphthoannulation and by the insertion of the electron-withdrawing substituent into the benzene ring (the latter weakens the intramolecular hydrogen bond in the compound). Substituent and naphtoannulation have no effect on the stability of the studied tautomers. Slight twisting of the benzene ring, with respect to the $C_{Ar}NC$ plane (seen in the crystalline state), was proven to also take place in vacuum and in solution.

Keywords: tautomerism; Gibbs free energies; iminodiketones; substituent effect; molecular structure; NBO

1. Introduction

Tautomerism plays a very important role in biochemistry, organic chemistry, pharmacology, and molecular biology. To understand the mechanisms of many chemical reactions and biological processes, we require an understanding of this phenomenon first. A low energy barrier between tautomers causes the process of tautomerization to be influenced by many external (e.g., temperature changes, solvent) and internal (structural) factors, such as: molecule structure, possible formation of intramolecular hydrogen bonds, introduction of a substituent to the molecule, or ring benzoannulation [1–3].

Knowledge of the structures of organic compounds, three-dimensional protein structures, and their complexes with ligands, is very important in drug design. Of course, crystallography and NMR are important tools for determining three-dimensional structures [4–8], but research is time-consuming and costly. The tools of structural bioinformatics ([9] and papers cited therein), whose rapid development led to an unprecedented revolution in medical chemistry [10], come to our aid. Computational biology plays an increasingly important role in stimulating the development of new drugs. Therefore, aside from experimental methods, computational methods have also been used in our research.

β-Amino-α,β-unsaturated ketones (enaminones) are known [11–27] to equilibrate with enolimines and ketiminones (Figure 1) [28]. Conformational and configurational isomerization of these compounds in solution is spontaneous [16–27,29]. The enaminone and enolimine forms can be stabilized by the intramolecular hydrogen bond, both in the solid state and in solutions in nonpolar solvents [15]. Although the N … H–O bond is usually stronger than the N–H … O one, the tautomeric species stabilized by the latter interaction are usually more stable [30–32]. Enaminone tautomers are stabilized by the hydrogen bonds, and their open forms are favored in non-polar and polar solvents [14]. Although liability of the species was found to be governed mainly by the changes in aromaticity of some molecular moieties, strength of the intramolecular hydrogen bond also contributes [33]. Benzoannulation is another factor that affects the stability of enaminones and their tautomers. Thus, only enolimine and ketiminone forms were detected when R1/R2 = benzo (Figure 1) [11]. Furthermore, benzoannulation of the pyridine ring in the molecules of these compounds at the 3,4- and/or 5,6-positions stabilizes the enaminone tautomer (enaminone) [12,13]. Numerous 3,4-benzoannulated enaminones are in equilibrium with the usually less stable [34,35] enolimine derivatives, i.e., N-salicylideneamines (enolimine, Figure 1, R^1 = Ar, R^2 = H, R^3/R^4 = benzo) [36–46]. Polar solvents, low temperatures, and benzoannulation, both at positions 2,3 and 4,5, favor the enaminone form [40,47–50]. Both experimental and ab initio calculations show that, in solution, *N*-salicylideneanilines (enolimines) are more stable than 2-[(phenylamino)methylene]cyclohexa-3,5-dien-1-ones (enaminones) [51]. The enaminone tautomer is the only form present in the crystalline state of *N*-(2-hydroxy-1-naphthylmethylidene)aniline [40] and the major form detected in solutions of *N*-(10-hydroxy-9-phenanthrylmethylidene)aniline [35]. Stabilization of enaminone in the crystalline state, results primarily from the intermolecular hydrogen bonding [52]. Changes in population of the enaminone and enolimine tautomers affect the thermochromic properties of numerous salicylideneanilines in their crystalline state, and in solution [30,34,52].

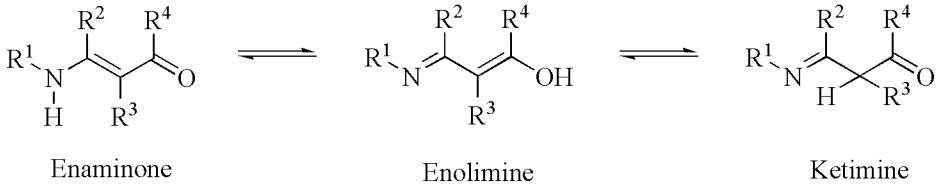


Figure 1. Enaminones and their tautomers.

Unstable 2-(diacylmethyl)pyridines (ketimine, Figure 1, R^1/R^2 = benzo, R^3 = acyl) should be considered as the acyl substituted 3-aminoacroleines [53]. Multinuclear NMR spectra show that only 3-(pyridin-2(1*H*)-ylidene)alkane-2,4-diones (enaminone, Figure 1, R^1/R^2 = benzo, R^3 = acyl) are present in chloroform solution (3-(pyridin-2-yl)alkane-2,4-diones and 3-hydroxy-2-(pyridin-2-yl)alk-2-enones were not detected) [53]. X-Ray data show that 2-(2(1*H*)-pyridinyliden)-1*H*-indene-1,3(2*H*)-dione, i.e., enaminone tautomer of 2-(pyridin-2-yl)-2*H*-indene-1,3-dione, was also the only form present in crystal. B3LYP/6-311g(2d,p) calculations show that the isolated molecule of this tautomer is generally more stable than that of the ketimine and enolimine forms [53].

Tautomeric preferences of 2-(anilinemethylidene)cyclohexane-1,3-dione were studied for the first time almost sixty years ago [54]. These compounds reveal interesting biological properties [55]. Owing to the presence of the nitrogen atom and two carbonyl groups in their molecules, *N*-(2,2-diacylvinyl)anilines are simply related to 1,2-dihydro-2,2-diacylmethylenequinolines, the enaminone tautomers of 2-(diacylmethyl)quinolines [53] (Figure 2). 2-(Anilinemethylidene)-cyclohexane-1,3-dione (**Ea** in Figure 3) is the only form present in solution (no 2-[(phenylimino)methyl]cyclohexane-1,3-dione (**K**) or non 3-hydoxy-2-((E)-(phenylimino)methyl)-cyclohex-2-enone (**O**) were detected) [56].

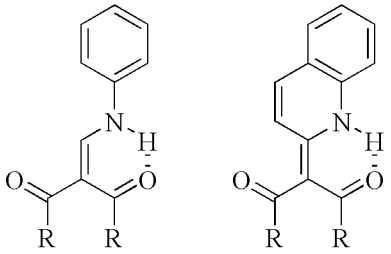


Figure 2. *N*-(2,2-diacylvinyl)anilines and 1,2-dihydro-2,2-diacylmethylenequinolines.

The substituent and naphthoannulation [57–59] are expected to affect the tautomeric preferences of these compounds [11–13]. Thus, ^{1}H and ^{13}C NMR experimental studies and quantum-chemical calculations were undertaken, to discover if some other (than those detected earlier) tautomers are stable enough to be present in solution.

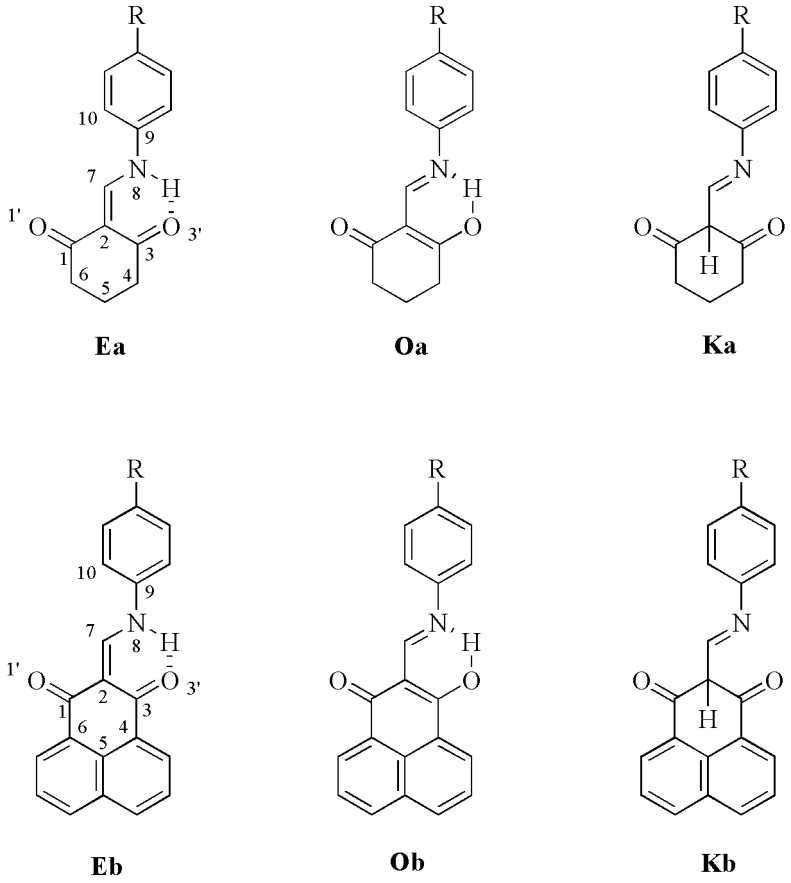


Figure 3. 2-(Anilinemethylidene)cyclohexane-1,3-diones, 2-(anilinemethylidene)-2*H*-phenalene-1,3-diones, and their tautomers (R = OMe (**1**), Me (**2**), H (**3**), Cl (**4**), NO2 (**5**)).

2. Materials and Methods

To make research clearer, easier to follow, and to predict results for similar systems, Chou's 5-step rule was followed [60]. Therefore, it was necessary to: (1) select or construct a valid benchmark dataset to train and test the predictor; (2) represent the samples with an effective formulation that truly reflects their intrinsic correlation with the target to be predicted; (3) introduce or develop a powerful algorithm to conduct the prediction; (4) properly perform cross-validation tests to objectively evaluate the anticipated prediction accuracy; and (5) establish a user-friendly web-server for the predictor that is accessible to the public. The advantages of this principle are: logic and transparency in action, the possibility for other researchers to repeat research, ease in developing methods and improving

shortcomings, and, most importantly, convenience for use by other researchers. Therefore, the role of Chou's 5-step method in conducting proteome/genome analyses, drug development, and research on bioorganic compounds, is unusual and amazing [61–71].

The graphical approach to the study of organic, biological, and medical systems, provides an intuitive understanding of the methodology and research results to the reader, and allows the reader to draw useful insights. Therefore, the methodology of our research is presented in Figure 4.

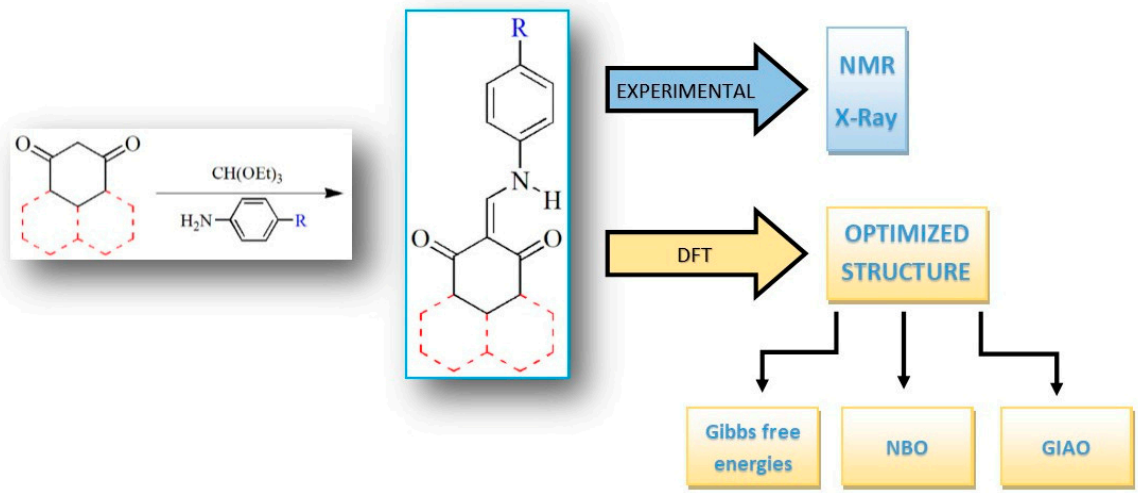


Figure 4. Materials used in research and methodology.

According to Figure 4, 2*H*-phenalene-1,3-dione was obtained from the commercially available 1,8-naphthalic anhydride [72]. 2-(Anilinemethylidene)cyclohexane-1,3-diones [73] and 2-(anilinemethylidene)-2*H*-phenalene-1,3-diones [74] were prepared in a 65–71% yield by the condensation of cyclohexane-1,3-dione and 2*H*-phenalene-1,3-dione, respectively, with substituted anilines and ethyl orthoformate. The crude reaction products were purified by recrystallization from ethanol (**1a**–**5a**) and dimethylformamide (**1b**–**5b**). Their pure crystalline forms melt at 130–133 °C; lit. mp. 132 °C [73] (**1a**), 104–105 °C (**2a**), 124–126 °C; lit. mp. 120°C [73], 124–125 °C [54] (**3a**), 154–156 °C; lit. mp. 144 °C [73] (**4a**), 213–215 °C (**5a**), 204–206 °C (**1b**), 222–224 °C (**2b**), 200–202 °C; lit. mp. 192 °C [75], 204–205 °C [76] (**3b**), 185–187 °C (**4b**), and 244–247 °C (**5b**). Satisfactory analytical data (±0.3% for C, H, and N) were obtained for all new compounds.

NMR spectra were recorded for 0.1–0.2 M solutions in DMSO-d_6 at 298 K with a Varian Gemini 200 NMR spectrometer working at 199.98 MHz for ^{1}H, and 50.28 MHz for ^{13}C. Both ^{1}H and ^{13}C NMR chemical shifts are referenced to internal TMS (δ = 0.00 ppm).

DFT calculations were performed using the Gaussian 16 software package [77]. An M06-2X [78] functional with def2TZVP [79,80] basis set were used. The Gibbs free energies were calculated for T = 298.15 K and P = 1 Atm. All computations were performed in the gas phase and in DMSO solution (dielectric constant ε = 46.7) using the conductor-like polarizable continuum solvation model (CPCM) [81,82]. NBO (Natural Bond Orbital) analyses were performed at the same level.

Theoretical chemical shifts for all E tautomers were calculated at the B3LYP/6-311G(d,p), using the standard GIAO (Gauge-Independent Atomic Orbital) procedure [83] for M06-2X/def2TZVP geometries (gas phase).

The DFT calculation results are available for download at https://repod.pon.edu.pl/pl/dataset/6dc02730-5c32-416c-bfea-4c2dcefa8268 [84].

3. Results and Discussion

Due to the very long relaxation times of quaternary carbon atoms, the respective signals were not observed in the NMR spectra. Unfortunately, as seen in Table 1, numerous chemical shifts for

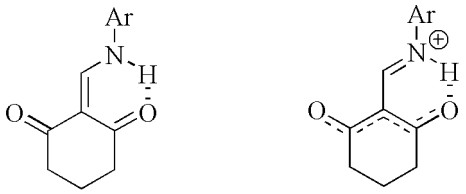
the compounds studied are lacking. The GIAO calculations come to our aid. The experimental and calculated values of chemical shifts in the NMR spectra correspond well with each other (Table 1).

^{13}C NMR chemical shift of C2 in typical 1,3-diketo systems is equal to 52–68 ppm [53,75,85,86]. A very weak signal in this range can be seen only in the ^{13}C NMR spectra of p-methoxy derivatives, **1Ka** (55.58 ppm) and **1Kb** (55.53 ppm). Thus, 2-[(phenylimino)methyl]cyclohexane-1,3-diones (**K**) are practically absent in DMSO solutions **1**–**5**. On the other hand, the separate C3 and C1 signals seen in the spectra of compounds **1a**, **2a**, **4a** and **5a** (Table 1) show that the respective **E** forms are present there [12,53]. The GIAO calculations confirm the experimental results. It can be effectively predicted that **3Ea** is also present in the DMSO solution. The values of the chemical shifts of C1 and C3 carbon for this tautomer are in the same range as the other "**a**" compounds. The carbonyl carbons in **1b** also resonate at different magnetic fields (Table 1). Since their signals are shielded, with respect to those seen in the spectra of compounds **1a**, **2a**, **4a** and **5a** (Table 1), one may assume that the order of the C1–O1′ and C3–O3′ bonds in **1Eb** is lower (longer bonds) than that in the other compounds studied. This implies that **1Eb** has an increased zwitterionic character (**Z** in Figure 5). Unfortunately, the signals of carbonyl carbons are not seen in the spectra of other compounds of this series, but one may assume that the molecules of **2Eb**–**5Eb** are even more zwitterionic. The GIAO analysis confirms this assumption. We can clearly see the shift of C1 and C3 signals in NMR spectra of **Eb** tautomers, which means they have more zwitterionic character than **Ea**.

Table 1. Selected ^{1}H and ^{13}C NMR chemical shifts (δ) for 1–5 in 0.1–0.2 M solutions in DMSO-d_6 at 298 K (regular font) and calculated using GIAO-B3LYP/6-311G(d,p) method (*italics*).

		H8	H7	C2	C7	C1	C3
1Ea	exp.	12.97d	8.55d	109.61	151.07	191.81	196.62
	calc.	*12.35*	*8.61*	*113.98*	*151.98*	*195.71*	*202.93*
1Eb	exp.	13.54d	8.90d	108.86	152.74	181.44	183.9
	calc.	*12.98*	*9.10*	*113.44*	*153.69*	*183.23*	*188.12*
2Ea	exp.	12.93d	8.61d	109.73	150.88	196.64	200.25
	calc.	*12.30*	*8.72*	*114.12*	*151.69*	*195.88*	*203.20*
2Eb	exp.	13.50d	8.96d	109.03	152.78	no	no
	calc.	*12.94*	*9.20*	*113.53*	*153.25*	*183.39*	*188.33*
3Ea	exp.	12.76d	8.58d	109.78	150.64	no	no
	calc.	*12.32*	*8.76*	*114.29*	*151.46*	*196.03*	*203.42*
3Eb	exp.	13.49d	9.00d	109.24	153.01	no	no
	calc.	*12.96*	*9.25*	*113.74*	*153.19*	*183.47*	*188.50*
4Ea	exp.	12.60d	8.47d	109.96	150.46	195.56	199.67
	calc.	*12.30*	*8.65*	*114.45*	*151.21*	*196.03*	*203.78*
4Eb	exp.	13.42d	8.96d	no	153.18	no	no
	calc.	*12.95*	*9.13*	*113.88*	*152.81*	*183.45*	*188.73*
5Ea	exp.	12.98d	8.47d	111.17	149.59	195.82	200.26
	calc.	*12.46*	*8.80*	*115.34*	*149.93*	*196.43*	*204.79*
5Eb	exp.	10.80bs	8.55bs	no	150.11	no	no
	calc.	*13.12*	*9.28*	*114.83*	*151.53*	*183.70*	*189.42*

d—doublet, bs—broad singlet. no—Signals of some quaternary carbon atoms were not observed in the spectrum of the saturated solution.



E **Z**

Figure 5. 2-(Arylaminemethylidene)cyclohexane-1,3-dione and its zwitterionic form.

H8 signals in the spectra of compounds **1b**–**4b** are seen at the significantly lower field, than those in the spectra of **1a**–**4a** (Table 1). Thus, the intramolecular hydrogen bonds in the former compounds are exceptionally strong. Similar effects to the naphthalene moiety on the chemical shift of acidic hydrogen atoms has been observed in some related compounds [53]. As shown by the significantly low chemical shift of H8 (Table 1), the intramolecular hydrogen bond in **5b** was exceptionally weak. Lack of the important ^{13}C chemical shifts (Table 1) precludes our ability to draw more detailed conclusions on its molecular structure. However, one may see that the very much differentiated effectiveness of the charge transfer in their molecules results in the significant differences in the zwitterionic character of **3Zb** and **5Zb** (Figure 6).

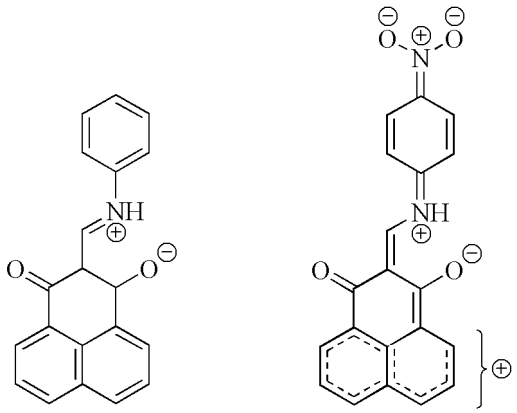


Figure 6. Zwitterionic forms of some compounds studied.

Zwitterionic character of the enaminone tautomer can be evaluated, at least in the crystalline state. The X-ray data show that the order of the C7–N8 single bond in **3Ea** is higher (≈1.7) than that of the C2=C7 double bond (≈1.5) [55]. Furthermore, the C1–C2 (1.455 Å) and C2–C3 (1.438 Å) bonds are significantly shorter than the standard C(sp^2)–C(sp^2) single bond (1.48 Å). On the other hand, both C3=O3′ (1.234 Å) and C1=O1′ (1.257 Å) carbonyl bonds are longer than the standard C=O bond (1.20–1.22 Å) [55]. These findings imply that there is an extensive π-electron transfer from N8 to the carbonyl groups, and proves that electron distribution in the molecule of **3Ea** reflects that shown in the zwitterionic resonance structure (**Z** in Figure 5). From this point of view, 2-(anilinemethylidene)cyclohexane-1,3-dione is similar to 3-(pyridin-2(1H)-ylidene)cycloalkane-2,4-diones [53]. X-ray measurements show that the benzene ring in the molecule of **3Ea** is slightly twisted, with respect to the $C_{Ar}NC$ moiety (C10C9N8C7 dihedral angle is equal to 16.2°) [55].

Density functional calculations are known to often be very helpful in the evaluation of the relative stability of different tautomers [13,53,87–89]. The results presented in Table 2 prove, that independently of substituent and series, the most stable form is always enaminone. Due to its very high value of Gibbs free energy, no one expected ketimine would equilibrate with this tautomer, both in vacuum and in DMSO solution. We can see a slight change in the stability of individual tautomers in vacuum and solution. Relative values of Gibbs free energies show that in DMSO solution, the respective **On**

tautomers are less stable than in vacuum. The opposite is true in the case of **Kn** tautomers, which are more stable in DMSO than in vacuum (Table 2).

Table 2. Calculated (M06-2X/def2-TZVP) relative [kcal/mol] Gibbs free energies for 2-(aniline-methylidene)cyclohexane-1,3-diones and its tautomers [a].

Form	G_{rel}		Form	G_{rel}	
	Vacuum	*DMSO*		Vacuum	*DMSO*
1Ea	0.0	*0.0*	**1Eb**	0.0	*0.0*
1Oa	5.5	*6.6*	**1Ob**	4.9	*6.0*
1Ka	20.0	*18.2*	**1Kb**	22.3	*20.9*
2Ea	0.0	*0.0*	**2Eb**	0.0	*0.0*
2Oa	5.9	*7.0*	**2Ob**	5.2	*7.4*
2Ka	20.5	*18.7*	**2Kb**	21.6	*22.3*
3Ea	0.0	*0.0*	**3Eb**	0.0	*0.0*
3Oa	5.4	*7.0*	**3Ob**	5.1	*6.1*
3Ka	19.7	*18.7*	**3Kb**	22.2	*20.8*
4Ea	0.0	*0.0*	**4Eb**	0.0	*0.0*
4Oa	5.3	*6.4*	**4Ob**	4.6	*5.6*
4Ka	19.4	*18.1*	**4Kb**	21.4	*20.1*
5Ea	0.0	*0.0*	**5Eb**	0.0	*0.0*
5Oa	5.6	*6.4*	**5Ob**	5.2	*5.7*
5Ka	19.2	*17.8*	**5Kb**	21.4	*20.1*

[a] Absolute values of Gibbs free energies are available in [84].

The optimized structure (Table 3) shows that lengths of the C3=O3′ and C1=O1′ bonds in **3Ea** are less differentiated than shown by the respective X-ray data [55]. The benzene ring in its molecule is slightly twisted with respect to the C7N8C9 plane (according to the X-ray data, this twisting was also observed in the crystalline state [55]—see comparison of X-ray data with DFT in Figure 7). The extent of this deformation increases for the more electron-donating substituents. It is considerably more significant in "**a**" compounds than in "**b**" compounds (Table 3).

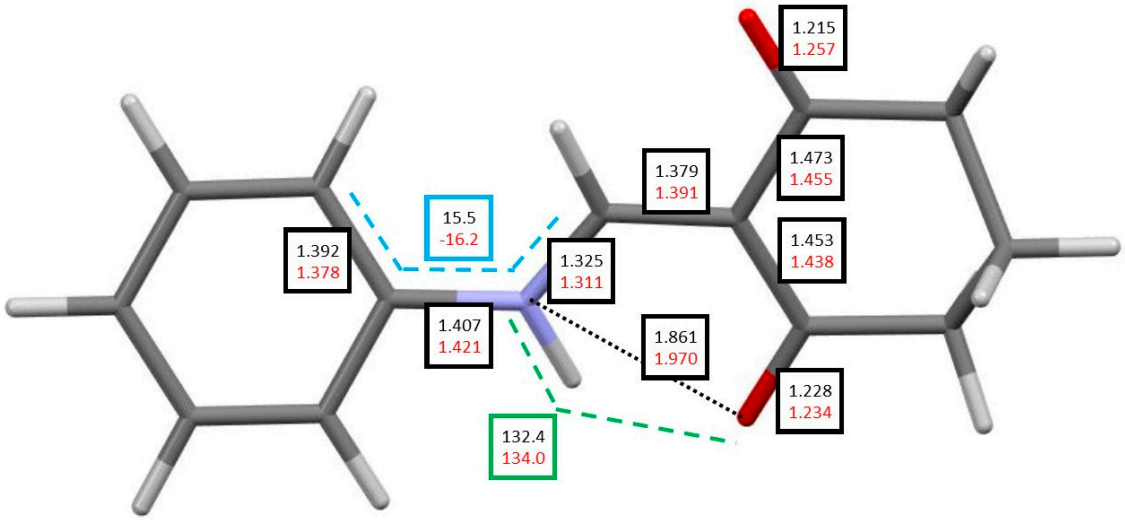


Figure 7. Comparison of geometric parameters (values of interatomic distances [Å]; angles and torsional angles [°]; corresponding black, green, and blue frames, respectively), for DFT (black font) and X-Ray [55] (red font) for **3Ea.**

Analyzing geometrical parameters of the studied tautomers (Table 3), we can observe that lengths of individual bonds in the vacuum and in DMSO are different. Namely, N8–C7, C2–C3, and

C2–C1 are shorter in DMSO than in vacuum; and N8–N9, C7–C2, C3–O3′, and C1–O1′ are longer in DMSO solution. This shows a slight change in the character of these bonds: N8–C7, C2–C3, and C2–C1 in DMSO obtain the characteristics of double bonds; and N8–N9, C7–C2, C3–O3′, and C1–O1′, characteristics of single bonds. This confirms that in DMSO, the studied **E** tautomers have more zwitterionic character (as shown in Figure 5). Additionally, the studied tautomers are stabilized by the intramolecular hydrogen bond N8–H8···O3′, which is shorter by 0.023–0.027 Å in vacuum.

Table 3. Optimized (M06-2X/def2-TZVP) bond lengths [Å], and bond and dihedral angles [deg] for selected 2-(anilinemethylidene)cyclohexane-1,3-diones in vacuum (regular font) and solution in DMSO (italics).

	1Ea	**3Ea**	**5Ea**	**1Eb**	**3Eb**	**5Eb**
N8–C7	1.322 *1.317*	1.325 *1.320*	1.333 *1.329*	1.321 *1.315*	1.324 *1.318*	1.332 *1.327*
N8–C9	1.409 *1.413*	1.407 *1.411*	1.396 *1.397*	1.409 *1.413*	1.406 *1.411*	1.495 *1.398*
C7–C2	1.382 *1.388*	1.379 *1.385*	1.372 *1.377*	1.382 *1.390*	1.379 *1.387*	1.372 *1.379*
C2–C3	1.451 *1.449*	1.453 *1.451*	1.458 *1.457*	1.447 *1.444*	1.449 *1.446*	1.454 *1.452*
C3–O3′	1.229 *1.234*	1.228 *1.232*	1.226 *1.230*	1.233 *1.237*	1.232 *1.236*	1.231 *1.233*
C2–C1	1.470 *1.464*	1.473 *1.466*	1.478 *1.472*	1.465 *1.458*	1.467 *1.461*	1.472 *1.466*
C1–O1′	1.215 *1.223*	1.215 *1.222*	1.213 *1.220*	1.219 *1.226*	1.219 *1.226*	1.217 *1.223*
N8–H8	1.021 *1.020*	1.021 *1.020*	1.021 *1.020*	1.022 *1.020*	1.021 *1.020*	1.022 *1.021*
H8···O3′	1.857 *1.884*	1.861 *1.887*	1.849 *1.873*	1.849 *1.875*	1.852 *1.875*	1.839 *1.862*
N8···O3′	2.656 *2.669*	2.659 *2.671*	2.653 *2.665*	2.650 *2.662*	2.652 *2.662*	2.645 *2.656*
N8H8O3′	132.5 *133.3*	132.4 *131.1*	133.0 *133.4*	132.6 *131.4*	132.5 *131.4*	133.2 *132.0*
C7N8C9C10	19.9 *22.7*	15.5 *19.9*	−2.3 *−6.8*	20.5 *23.5*	16.2 *18.7*	3.1 *9.1*

The second order Fock matrix was carried out to confirm the charge transfer in studied systems in the NBO analysis. The calculated stabilization energies (E(2)) [90] for the selected donor (i) –acceptor (j) interactions corresponding to i→j electron delocalization, are shown in Table 4. They confirm that there is charge transfer in all studied systems. The higher the E(2) value, the more intense the donor–acceptor interaction is.

Table 4. Calculated stabilization energies (E(2)) for selected donor (i) –acceptor (j) interactions in the studied tautomers.

Tautomer	Donor (i)	Type	Acceptor (j)	Type	E(2) [kJ/mol]	
					Vacuum	DMSO
1Ea	N8	LP	C7–C2	π*	88.85	95.36
	C7–C2	π	C3–O3′	π*	39.92	42.07
	C7–C2	π	C1–O1′	π*	33.13	37.43
3Ea	N8	LP	C7–C2	π*	85.37	91.48
	C7–C2	π	C3–O3′	π*	38.65	40.77
	C7–C2	π	C1–O1′	π*	32.30	36.43
5Ea	N8	LP	C7–C2	π*	76.48	80.29
	C7–C2	π	C3–O3′	π*	35.82	37.30
	C7–C2	π	C1–O1′	π*	29.77	33.35
1Eb	N8	LP	C7–C2	π*	88.47	96.54
	C7–C2	π	C3–O3′	π*	41.96	a
	C7–C2	π	C1–O1′	π*	35.16	40.08
	C7–C2	π	C3	LP*	a	73.06
3Eb	N8	LP	C7–C2	π*	85.00	93.05
	C7–C2	π	C3–O3′	π*	40.68	43.63
	C7–C2	π	C1–O1′	π*	34.31	39.03
5Eb	N8	LP	C7–C2	π*	75.86	81.63
	C7–C2	π	C3–O3′	π*	37.67	40.11
	C7–C2	π	C1–O1′	π*	31.68	35.90

a—not observed.

Based on E(2) values, we can see that in DMSO solution, the charge transfer in **E** tautomers is more effective (in DMSO solutions, **E** tautomers are more zwitterionic in character, than in vacuum). It can be also observed that the intensity of electron transfer is highest for compounds with strong electron-donating substituent (-OMe) in the benzene ring (**1Ea** and **1Eb**). The naphthoannulation of diketone moiety has a slight influence on the electron transfer of N8(LP)→C7–C2(π*); E(2) values for the respective **Ea** and **Eb** are similar. On the other hand, the delocalization of the electrons C7–C2(π)→C3–O3′(π*) and C7–C2(π)→C1–O1′(π*) is more effective for "**b**" compounds. In the case of the compound **1Eb** in DMSO, a strongly stabilizing (73.06 kJ/mol) charge transfer to carbonyl carbon atom C3 was found.

The calculated NBO charges (Table 5) also confirm that in DMSO solutions all the **E** forms are more zwitterionic than in vacuum. In general, charge separation in "**b**" compounds is more effective than in "**a**" compounds.

Table 5. NBO charges (M06-2X/def2-TZVP) for selected 2-(aniline-methylidene)cyclohexane-1,3-diones in vacuum (regular font) and solution in DMSO (italics).

	N8	O3′	O1′
1Ea	−0.514	−0.628	−0.463
	−0.500	*−0.660*	*−0.640*
3Ea	−0.520	−0.623	−0.583
	−0.508	*−0.655*	*−0.636*
5Ea	−0.528	−0.613	−0.572
	−0.517	*−0.642*	*−0.623*
1Eb	−0.510	−0.635	−0.591
	−0.493	*−0.660*	*−0.638*
3Eb	−0.516	−0.630	−0.587
	−0.501	*−0.656*	*−0.634*
5Eb	−0.525	−0.622	−0.578
	−0.511	*−0.644*	*−0.623*

4. Conclusions

2-[(phenylimino)methyl]cyclohexane-1,3-diones are practically absent in DMSO solutions. On the other hand, their enaminone tautomers, i.e., 2-(anilinemethylidene)cyclohexane-1,3-diones, were detected by ^{1}H and ^{13}C NMR spectroscopy. DFT calculations prove that aside from substituent, the most stable form is always enaminone. Naphthoannulation of the said enaminones results in effective intramolecular charge transfer. Thus, 2-(anilinemethylidene)-2*H*-phenalene-1,3-diones have a significant zwitterionic character. This effect is most distinct in the molecule of the respective p-nitro derivative. Optimization procedures (M06-2X/def2-TZVP) show that lengths of the bonds in 2-(anilinemethylidene)-cyclohexane-1,3-dione are less differentiated than shown in the X-ray data. Unexpectedly, the optimized geometries of the more and less zwitterionic tautomers are comparable. The NBO studies show that, in general, 2-(anilinemethylidene)cyclohexane-1,3-diones are less zwitterionic than their naphtho derivatives.

Author Contributions: Conceptualization, R.G. and R.D.; methodology, R.G. and R.D.; software, R.D.; validation, R.G. and J.M.; formal analysis, R.G.; investigation, R.D. and R.G.; resources, R.G.; data curation, J.M.; writing—original draft preparation, R.G. and R.D.; writing—review and editing, R.G., R.D., and J.M.; visualization, J.M. and R.D.; supervision, R.G.; project administration, R.D.; funding acquisition, J.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Acknowledgments: R.D. is very much indebted to CI TASK Gdańsk, for their supply of computer time and programs.

Conflicts of Interest: The authors declare no conflict of interest.

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