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ORIGINAL PAPER

Effect of benzoannulation on tautomeric preferences of 4,6-di(pyridin-2-yl)cyclohexane-1,3-dione

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Abstract Density functional theory (DFT) calculations at the B3LYP/6-311+G(d,p) level show that 4,6-di(pyridin-2-yl)cyclohexane-1,3-dione is a labile compound. On the other hand, its dienolimine tautomer (4,6-di(pyridin-2-yl)cyclohaxa-1,3-diene-1,3-diol) seems stable enough to be present in vacuum. Alternatively the equilibriated species are (i) dienolimine and enolimine-enaminone ((6*Z*)-3-hydroxy-6-(pyridin-2(1*H*)-ylidene)-4-(pyridine-2-yl)cyclohex-3-enone) or (ii) dienolimine, enolimine-enaminone and dienaminone ((4*Z*,6*Z*)-4,6-di(pyridin-2(1*H*)-ylidene)cyclohexane-1,3-dione). Benzoannulation of the pyridine ring at position 5,6 was found to increase the contribution of the tautomers which contain the enaminone moiety. Energies of the transition states between the stable tautomers were also calculated in order to estimate activation energy of the proton transfer. Values of the geometry based harmonic oscillator model of aromaticity (HOMA) index and Laplacian of the electron density in the hydrogen bond critical point (based on quantum theory of atom in molecules) shows that the enaminone moiety in the tautomers studied are stabilized by stronger intramolecular hydrogen bond than this present in the enolimine moiety.

Keywords Benzoannulation · DFT · 1,3-Diketones · Pyridines · Tautomerizm · Transition states

Introduction

1,3-Dicarbonyl compounds are generally in equilibrium with the respective ketoenols [1]. On the other hand, their pyridin-2-yl derivatives equilibrate with the respective enolimine and enaminone tautomers [2–4]. Except the β-diketo species, all other forms mentioned are stabilized by the intramolecular hydrogen bonds and by the resonance [1]. Quantum-chemical calculations confirm these tautomers to be energetically preferred [2–4]. 4,6-Di(pyridin-2-yl)cyclohexane-1,3-dione (**1**, Scheme 1), its mono, 4-(pyridin-2-yl)-6-(quinolin-2-yl)cyclohexane-1,3-dione (**2**), and dibenzo, 4,6-di(quinolin-2-yl)cyclohexane-1,3-dione (**3**), derivatives are other compounds of that type being of interest to us from the tautomeric point of view. Since the 3-hydroxycyclohexanone moiety present in their molecules does not allow the respective ketoenol tautomers to be stabilized by the intramolecular hydrogen bond, the number of possible products of proton transfer is not as high as for their acyclic analogues. The goal of the present paper is to show the tautomeric preferences in such special systems.

Although compounds **1**–**3** are not known, their properties seem worthy to be studied in order to draw general conclusions concerning the effect of structure on complex tautomeric equilibria in pyridin-2-yl derivatives of β-diketones [2–4]. Such a phenomenon plays a vital role in many important chemical and biological processes. For example, double proton transfer occurs in DNA base pairs such as the adenine-

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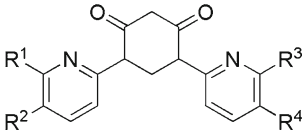


Scheme 1 The formula of 4,6-di(pyridin-2-yl)cyclohexane-1,3-diones. R^1/R^2 and R^1/R^2 = H/H and H/H (**1**), H/H and benzo (**2**), benzo and benzo (**3**)

thymine base pair [5]. A wide range of enzyme reactions, including serine proteases [6, 7], alcohol dehydrogenases [8], and carbonic anhydrases [9], require multiple proton transfer reactions.

Computational details

Geometry optimizations for the tautomers and transition states were performed using Gaussian 03 software package [10]. The hybrid functional B3LYP [11, 12] and 6-311+G(d,p) basis set [13] were used. The vibrational frequencies were obtained to make sure that geometry is in minimum (no imaginary frequencies were found for all stable systems; one or two frequencies were negative for the transition states between two tautomers that differ by location of one or two hydrogen atoms, respectively). Calculations were performed for the isolated systems.

Equation (1) was used to evaluate the tautomeric constants (tautomeric constants for the **A⇌B** equilibrium is defined as K_T=[**B**]/[**A**]). The Gibbs free energies (G) are those calculated at B3LYP/6-311+G(d,p) level of theory (T=298.15 K, P=1 Atm, R – gas constant).

$$K_T = e^{\frac{-\Delta G}{RT}} \tag{1}$$

The bond lengths in the optimized tautomers were used to estimate the geometry-based aromaticity index HOMA [14, 15] defined in Eq. 2.

$$HOMA = 1 - \frac{1}{n}\sum_{j=1}^{n} \alpha_i \left(R_{opt,i} - R_j\right)^2 \tag{2}$$

n represents the total number of bonds in the molecule, α_i is just the normalization constant (for CC, CO, and CN bonds α=257.7, 157.38 and 93.52, respectively). It is fixed to give HOMA=0 for the model non-aromatic system, *e.g.*, Kekule benzene and HOMA=1 for the system with all bonds equal to the optimal value $R_{opt,i,}$ assumed to be realized for fully aromatic systems ($R_{opt,\ CC}$=138.8 pm, $R_{opt,\ CN}$=133.4 pm and $R_{opt,\ CO}$=126.5 pm).

Topological analysis of electron density was evaluated within the quantum theory of atom in molecule (QTAIM) model [16] using the B3LYP/6-311+G(d,p) wave functions. The critical points (BCP) were found for the hydrogen bonds studied. Electron density at BCP (ρ_{BCP}) and its Laplacian ($\nabla^2\ \rho_{BCP}$) were analyzed.

Results and discussion

The compounds studied contain three acidic hydrogen atoms (H3/3′ and H6) and four basic centers (N1/1′ and O5/5′). Due to numerous potential proton transfers in their molecules, 4,6-di(pyridin-2-yl)cyclohexane-1,3-dione (**1**) and its dibezo derivative **3** may equilibrate with 12 different tautomers. Loss of symmetry by the molecule of the respective mono benzo derivative **2** is responsible for increase of this number to 21. The formulas of some of these tautomers are presented in Scheme 2 (the complete set of possible tautomeric forms, as well as their absolute and relative energies can be found in Supplementary materials). As this can be seen in Table 1, the relative free Gibbs energies of these forms, with respect to the most stable form, are less than 10 kcal mol^{-1}.

Scheme 2 The most stable tautomeric forms of **1**–**3**. Following abbreviations were used for the respective moieties: **P** – pyridine, **Q** – quinoline, **E** and **E'** – 1,2-dihydropyridine (enamine), **K** – ketone, **O** – enol

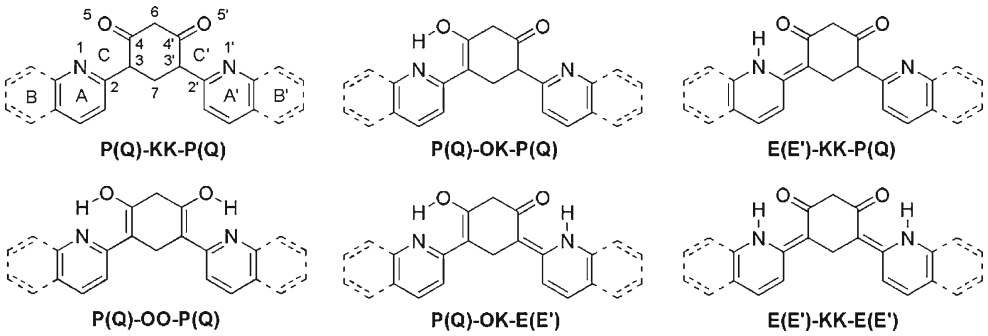


Table 1 Calculated relative Gibbs free energies (G_{rel}) [kcal mol^{-1}] of the energetically most stable tautomeric forms of 4,6-di(pyridin-2-yl)cyclohexane-1,3-dione (**1**), 4-(pyridin-2-yl)-6-(quinolin-2-yl)cyclohexane-1,3-dione (**2**) and 4,6-di(quinolin-2-yl)cyclohexane-1,3-dione (**3**). Expected contributions of the respective tautomers are given in parentheses

1		2		3	
Tautomers	G_{rel}	Tautomers	G_{rel}	Tautomers	G_{rel}
P-OO-P	0.00[a] (99 %)	**P-OK-E′**	0.00[b] (57 %)	**Q-OK-E′**	0.00[c] (38 %)
P-OK-E	2.55 (1 %)	**P-OO-Q**	0.17 (42 %)	**E′-KK-E′**	0.04 (36 %)
P-OK-P	3.98	**Q-OK-E**	2.74	**Q-OO-Q**	0.22 (26 %)
E-KK-E	4.79	**E′-KK-P**	3.16	**E′-KK-Q**	3.44
E-KK-P	5.81	**Q-OK-P**	4.16	**Q-OK-Q**	4.39
P-KK-P	6.35	**E-KK-E′**	4.25	**Q-KK-Q**	7.68
		P-OK-Q	4.35		
		E-KK-Q	6.21		
		P-KK-Q	6.96		

[a] Absolute Gibbs free energy: -878.100154 Hartree

[b] Absolute Gibbs free energy: -1031.738160 Hartree

[c] Absolute Gibbs free energy: -1185.375697 Hartree

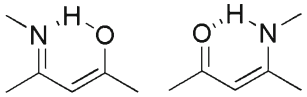
Transfer of H3/3′ in the **P(Q)-KK -P(Q)** forms to O5/5′ or to N1/1′ results in formation of the enolimine, **P(Q)-O**, or enaminone, **E(E′)-K**, moieties, respectively, both being stabilized by the intramolecular hydrogen bonds. On the other hand, similar interaction, *i.e.*, OH···O=C, is not possible in the ketoenol moiety formed by "shifting" of H6 to the carbonyl oxygen. As a consequence, such tautomers have relatively high energies (Supplementary material) and do not contribute to the tautomeric mixture.

Among different dipyridine tautomers possible, the **P-OO-P** form was found to be energetically most stable in vacuum (Table 1). Both mono- and dibenzo annulation do not change the tautomeric preference: contributions of the respective tautomers are still high (42 % and 26 %, respectively). As this was expected, extension of the aromatic system in the molecule results in stabilization of the **E** moieties (Table 1).

As can be seen in Table 2, activation energies of proton transfers between the tautomers, E_a, are in general equal to 2.9-3.2 kcal mol^{-1}. The equilibrium between **P-OO-P** and **P-OK-E** is an exception: E_a=4.3 kcal mol^{-1}. This increased barrier to the rearrangement and low tautomeric constant, K_T=0.01, support exceptional character of the **P-OO-P** form (the tautomers are expected to contribute). Both K_T=0.76 and low values of the proton transfer activation energy (E_a=2.9 kcal mol^{-1}) for the equilibrium between **P-OO-Q** and **P-OK-E′** (Table 2) shows that the respective proton transfer proceeds easily. As a consequence, each of these tautomers contributes significantly (Table 1). $\Delta G>0$ and low value of K_T (Table 2) show that proton transfer between the dibenzo annulated **Q-OK-E′**, **E′-KK-E′** and **Q-OO-Q** species is quite easy. Thus, all three tautomers are expected to equilibriate between themselves. As expected, the mutual

Table 2 Calculated Gibbs free energies of the proton transfers, tautomeric constants, K_T=[**B**]/[**A**] and proton transfer activation energies E_a

A⇌B	G_A [Hartree]	G_B [Hartree]	ΔG [kcal mol^{-1}]	K_T	E_a [kcal mol^{-1}]
P-OO-P⇌P-OK-E	−878.100154	−878.096091	2.55	0.01	4.3
P-OK-E′⇌P-OO-Q	−1031.738160	−1031.737897	0.17	0.76	2.9
Q-OK-E′⇌E′-KK-E′	−1185.375697	−1185.375641	0.04	0.94	3.2
Q-OK-E′⇌Q-OO-Q	−1185.375697	−1185.375347	0.22	0.69	2.9
E′-KK-E′⇌Q-OO-Q	−1185.375641	−1185.375347	0.18	0.73	5.9



Scheme 3 Intramoleculer hydrogen bonds bonds present in enolimines and enaminones

transformation of **E′-KK-E′** and **Q-OO-Q** (double proton transfer) is a difficult process (E_a=5.9 kcal mol^{-1}, Table 2).

Hydrogen bonds in the H−O−C=C−C=N and O=C−C=C−N−H systems (Scheme 3) enables the quasirings to be present in some tautomers discussed. The NH···O hydrogen bond in **P-OK-E** is by *ca* 5 pm shorter than OH···N in **P-OK-P** and **P-OO-P** (Table 3). On the other hand, the later bond was found to be shorter in the mono- and dibenzo annulated tautomers.

However, the Laplacian values of electron density in the bond critical point ($\nabla^2\rho_{BCP}$) being equal to 0.115-0.117 a.u. and 0.151-0.159 a.u. for the OH···N and NH···O bonds, respectively (Table 3) clearly show that the later (being present in the enaminone moieties) is stronger.

Strength of the hydrogen bonds can be also confirmed by the calculated HOMA values (Table 4). These parameters are equal to 0.39-0.44 and 0.84-0.86 for the quasirings stabilized by the OH···N and NH···O bonds, respectively. Although both of them are of resonance assisted hydrogen bond (RAHB) type [17–20], the later seems to be more strong.

Tautomeric preferences observed may be partially explained by the Clar rule [21, 22]. The HOMA values (Table 4) show that in the enolimine moiety of pyridyn-2-yl derivatives only the pyridine ring is fully aromatic. On the other hand, in the enaminone moiety this ring and (quasi)ring follow the topological naphthalene-like motif

Table 3 Characteristics of two different hydrogen bonds in different tautomers studied

Tautomer	Hydrogen bond	$d_{H...O}$ or $d_{H...N}$[a] [pm]	ρ_{BCP}[b] [a.u.]	$\nabla^2\rho_{BCP}$[c] [a.u.]
P-OO-P	OH···N	165.8	0.061	0.116
	OH···N	165.8	0.061	0.116
P-OK-E	OH···N	165.8	0.061	0.117
	NH···O	160.4	0.063	0.159
P-OO-Q	OH···N	165.4	0.061	0.116
	OH···N	163.5	0.064	0.115
P-OK-E′	OH···N	165.4	0.061	0.117
	NH···O	166.3	0.054	0.156
Q-OK-E′	OH···N	163.8	0.064	0.115
	NH···O	166.5	0.054	0.156
E′-KK-E′	NH···O	165.5	0.050	0.151
	NH···O	165.5	0.050	0.151
Q-OO-Q	OH···N	163.6	0.064	0.115
	OH···N	163.6	0.064	0.115

[a]Distance between H and O or between H and N

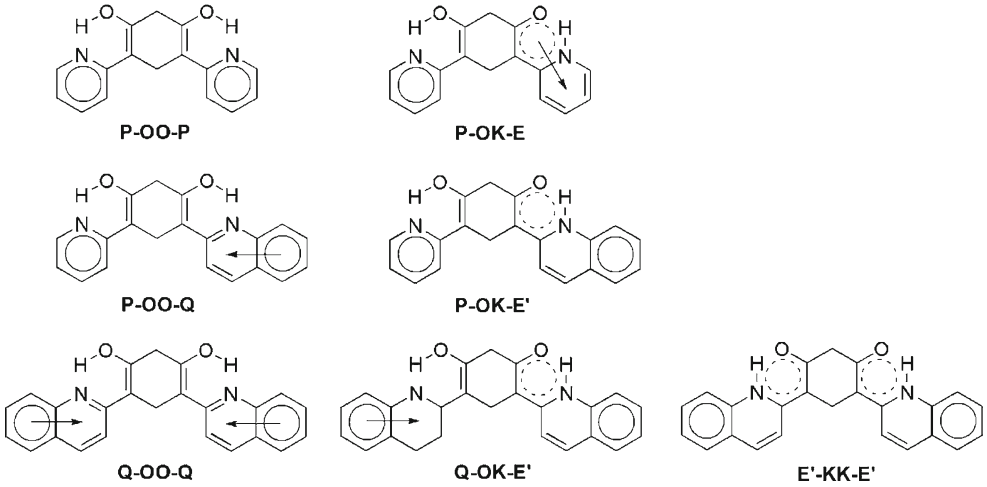
[b]Electron density in the bond critical point

[c]Laplacian of electron density in the bond critical point

Table 4 The HOMA values (B3LYP/6-311+G(d,p)) for the (quasi)rings present in different tautomers studied (for the ring symbols see Scheme 2)

Tautomer	HOMA A	HOMA B	HOMA C	HOMA A'	HOMA B′	HOMA C′
P-OO-P	0.96	-	0.39	0.96	-	0.39
P-OK-E	0.96	-	0.39	0.83	-	0.86
P-OO-Q	0.96	-	0.39	0.78	0.83	0.44
P-OK-E′	0.96	-	0.39	0.67	0.92	0.85
Q-OK-E′	0.78	0.83	0.43	0.67	0.92	0.85
E′-KK-E′	0.67	0.92	0.84	0.67	0.92	0.84
Q-OO-Q	0.78	0.83	0.43	0.78	0.83	0.43

Scheme 4 Graphical illustration of the Clar rule for the studied



with migration of the Clar sextet to the A′ and C′ rings (Scheme 4). The same motif can be seen for the A(A′) and B(B′) rings in the enolimine moieties of quinolin-2-yl derivatives. On the other hand, the (quasi)rings B(B′), A(A′) and C(C′) in the respective enaminone tautomers follow the phenanthrene-like motif with the empty inner ring A(A′), fully aromatic outer ring B(B′) and (quasi)ring C(C′) (Scheme 4). Thus, one can see that there is only one π-electron sextet, *i.e.*, this present in the pyridine ring, in the energetically preferred **P-OO-P** tautomer. As this was expected, benzene ring(s) change the tautomeric preferences. The enaminone **P-OK-E′**, **Q-OK-E′** and **E′-KK-E′** tautomers contain two π-electron sextets assigned to the A(A′), B(B′) and C(C′) (quasi)rings (in benzenoid hydrocarbons the π-electrons participating in the aromatic sextets should be assigned to the particular rings in such a way to obtain the maximum number of π-electron sextets [23]). On the other hand, in the mono- and dibenzo annulated enolimine tautomers only one π-electron sextet is assigned to the A(A′), B(B′) and C(C′) (quasi)rings, and therefore contribution of these forms is low.

Conclusions

DFT studies of the proton transfer process in the 4,6-di(pyridin-2-yl)cyclohexane-1,3-dione molecule shows that among its different tautomers, dienolimine (4,6-di(pyridin-2-yl)cyclohexa-1,3-diene-1,3-diol) is the most stable. Mono- and dibenzoannulation of the pyridine ring(s) results in an increase of the contribution of the enaminone species. As this was supported by the geometry based HOMA index and Laplacian of the electron density in hydrogen bond critical point, of two different hydrogen bonds that may stabilize the respective tautomers, *i.e.*, N−H…O and N…H−O, the former is stronger. The Clar rule was also found helpful in estimation of the tautomeric preferences of 4,6-di(pyridin-2-yl)cyclohexane-1,3-dione and its benzologs.

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