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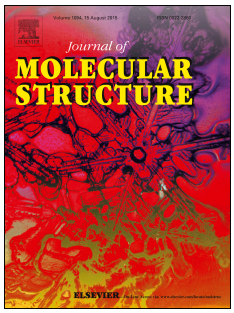

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Agnieszka Skotnicka, Przemysław Czeleń, Ryszard Gawinecki

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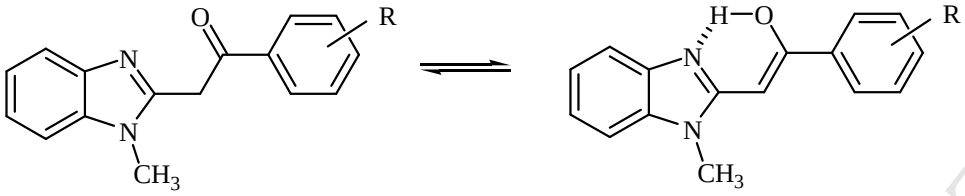
Graphical abstract



K **O**

R = *p*-N(CH_3)$_2$ (**1**), *p*-OCH_3 (**2**), *p*-CH_3 (**3**), *m*-CH_3 (**4**), H (**5**), *p*-Br (**6**), *m*-Cl (**7**), *p*-NO_2 (**8**)

Tautomeric Equilibria in Solutions of 1-Methyl-2-Phenacylbenzimidazoles

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Abstract: Until now the susceptibility of 1-methyl-2-phenacylbenzimidazoles to the proton transfer has not been carefully examined. There only have been selective trials to recognize tautomeric equilibrium of substituted compounds. Unfortunately, conclusions of these studies are often conflicting. Therefore, the aim of this work was to analyze the influence of the factors affecting the tautomeric processes of substituted 1-methyl-2-phenacylbenzimidazoles in solutions of chloroform by spectroscopic technique of ^{1}H and ^{13}C NMR. Complex equilibria may only take place when molecules of tautomeric species contain multiple basic and/or acidic centres. Analysis of NMR spectra show unequivocally that 1-methyl-2-phenacyl-benzimidazoles (ketimine tautomeric form) are in equilibrium with (*Z*)-2-(1-methyl-1*H*-benzo[*d*]imidazol-2yl)-1-phenylethenols (enolimine).

Keywords: phenacylbenzimidazoles, tautomerism, substituent effect, hydrogen bond, NMR, quantum-chemical calculations.

Introduction

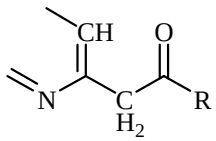
Benzimidazoles and imidazoles are widely used as the substrates in synthesis of organic compounds, mostly heterocyclic [1]. Derivatives of benzimidazoles deserve attention because these compounds show significant biological activity [2]. They act, *e.g.*, in the

antibacterial way [3,4], destroy parasites [5], are antiallergic [6] and show anti-tumour action [7]. Besides, a fragment of 5,6-dimethylbenzimidazole is a component of vitamin B_{12} [8].

Some of 1-methyl-2-phenacylbenzimidazoles were synthesized according to reaction of benzoyl substituted mercaptals with *N*-methyl-*o*-phenylenediamine [9,10]. Unfortunately, the synthesis requires a usage of relatively inconvenient substrates and with the release of methanethiol. Aforementioned synthesis, as well as other earlier described in the literature [11,12], are characterized by low yield, therefore, we prepared compounds **1**,**7** and **8** according to slightly modified reaction using 1,2-dimethylbenzimidazole with substituted ethyl or methyl benzoate and excess of sodium hydride [1]. On the other hand, compounds **2**-**6** were prepared by using a method based on conversion of 2-phenacylbenzoxazoles [13] and 2-phenacylbenzimidazoles [14].

Until now the susceptibility of 1-methyl-2-phenacylbenzimidazoles to the proton transfer has not been carefully examined. There have been selective trials to recognize tautomeric equilibrium of substituted compounds. Unfortunately, conclusions of these studies are often conflicting. In the majority of cases, the literature reports reveal that 1-methyl-2-phenacylbenzimidazoles (ketimine) are in equilibrium with enaminone tautomers [9-12,14]. However, some studies [15] suggest that these compounds occur only in enolimine form. Therefore, divergence and insufficient literature data led us to investigate factors influencing tautomeric equilibria in solutions of 1-methyl-2-phenacylbenzimidazoles.

Complex equilibria may only take place when molecules of tautomeric species contain multiple basic and/or acidic centres. 2-acylmethylpyridines are capable of being transformed into their tautomers [16-21]. The molecules of these compounds contain a specific moiety (Scheme 1) that enables transfer of the methylene proton to the oxygen and nitrogen atoms (basicity centres).



Scheme 1. 4-(Methyleneamino)hex-4-en-2-one moiety

This particular moiety is also present in some other phenacyl substituted heterocycles. Recently, we found that 2-phenacylbenzoxazoles (ketimine form) are in equilibrium with (*Z*)-2-(benzo[*d*]oxazol-2-yl)-1-phenylethenols (enolimine form) in chloroform ($CDCl_3$) solutions [13]. Molar ratio of these tautomers depends significantly on substitution. Thus, the strong

electron-donating substituents were found to stabilize the ketimine tautomer. The MP2 *ab initio* calculations supported our experimental finding, where the enolimine tautomer with the intramolecular OH···N hydrogen bond was observed to be more stable than enaminone, *i.e.*, (*E*)-2-(benzo[*d*]oxazol-2(3*H*)-ylidene)-1-phenylethanone. ^{13}C CPMAS NMR spectral data revealed that the *p*-NMe_2-substituted ketimine tautomer is the only form present in the crystalline state. On the other hand, in our studies enolimine form was detected when the substituent has either an electron-donor character or electron-acceptor one [13].

It is well known that minor modifications in the molecule may significantly affect the tautomeric equilibria [13,16,17,21,22]. This work describes chemical experiments and quantum-chemical calculations to determine tautomeric equilibria recorded in $CDCl_3$ solutions of 1-methyl-2-phenacylbenzimidazoles. The detailed methodologies used to prepare material for NMR spectra and then theoretical studies have been considered in the following section.

Material and Methods

1,2-dimethylbenzimidazole was prepared by the known method [23]. Other used substrates were purchased from Sigma-Aldrich. Melting points were measured on a Boetius table and are uncorrected. Satisfactory elemental analyses (± 0.30 % for C, H and N) were obtained for all prepared compounds.

Syntheses

Slightly modified procedure [9] was used to prepare compounds **1**,**7** and **8**. Thus, a mixture of 1,2-dimethylbenzimidazole (0.29 g, 2 mmol), substituted ethyl or methyl benzoate (2 mmol), dry benzene (10 mL), dimethylformamide (0.5 mL) and sodium hydride (0.15 g of its 60% suspension in mineral oil) was refluxed and stirred magnetically overnight. The reaction was quenched by addition of water (15 mL) and the resulted mixture was extracted with ethyl acetate (20 mL). The organic layer was subsequently washed with water (2 x 10 mL) and brine (2 x 10 mL) and dried with sodium sulfate. Solid impurities were filtered off, the filtrate was concentrated on the rotary evaporator and the obtained solid was recrystallized from ethanol.

On the other hand, compounds **2**-**6** were prepared by treating 1,2-dimethylbenz-imidazole with benzoyl chlorides in the presence of triethylamine followed by thermal decomposition of formed 2-(1-methyl-1*H*-benzo[d]imidazol-2-yl)-1-phenylvinyl benzoates.

Thus, substituted benzoyl chloride (8 mmol) was added at once to the mixture of 1,2-dimethylbenzimidazole (0.29 g, 2 mmol), triethylamine (0.81 g, 8 mmol) and diglyme (10 mL) and the resulted mixture was heated (steam bath) and stirred overnight. Addition of water (6 mL) precipitated the byproduct. Solution of morfoline (0.52 g, 6 mmol) in methanol (3 mL) was added to crude 2-(1-methyl-1*H*-benzo[d]imidazol-2-yl)-1-phenylvinyl benzoate and the resulted mixture was refluxed for 5 minutes. Reaction was quenched by addition of water (3 mL) and the precipitated solid product was recrystallized from ethanol.

Products characteristics are compiled in Table 1. Here there is an elemental analysis of the aforementioned compounds:

1: $C_{18}H_{19}N_3O$ (293.36): calcd. C 73.69, H 6.53, N 14.32; found C 73.54, H 6.41, N 14.39.

2: $C_{17}H_{16}N_2O_2$ (280.32): calcd. C 72.84, H 5.75, N 9.99; found C 72.91, H 5.65, N 9.86.

3: $C_{17}H_{16}N_2O$ (264.32): calcd. C 77.25, H 6.10, N 10.60; found C 77.12, H 6.23, N 10.67.

4: $C_{17}H_{16}N_2O$ (264.32): calcd. C 77.25, H 6.10, N 10.60; found C 77.17, H 6.16, N 10.54.

5: $C_{16}H_{16}N_2O$ (250.3): calcd. C 76.78, H 5.64, N 11.19; found C 76.83, H 5.66, N 11.23.

6: $C_{16}H_{13}BrN_2O$ (329.19): calcd. C 58.38, H 3.98, N 8.51; found C 58.31, H 3.96, N 8.47.

7: $C_{16}H_{13}ClN_2O$ (284.74): calcd. C 67.49, H 4.60, N 9.84; found C 67.52, H 4.62, N 9.94.

8: $C_{16}H_{13}N_3O_3$ (295.29): calcd. C 65.08, H 4.44, N 14.23; found C 65.09, H 4.42, N 14.21.

NMR spectra

The ^{1}H and ^{13}C NMR spectra were recorded for diluted $CDCl_3$ solutions at 298 K on a Bruker Avance 400 FT NMR spectrometer. The chemical shifts are referenced to the signal of internal TMS at δ=0.00 ppm. The solid state ^{13}C CPMAS (cross-polarization, magic angle spinning) NMR spectra were recorded on the same spectrometer using the samples packed in 4.0 mm o.d. zirconia rotors. The samples were spun at 12 kHz rate and >1000 transients were accumulated. The acquisition time for compound **2** was 0.034 sec and for compound **8** was 0.025 sec. The FIDs are apodized by 10 Hz exponential window before FT. The shifts are referenced to the C=O signal of glycine standard at δ = 176.03 ppm. Spectra are available in Supplementary material.

Quantum-chemical calculations

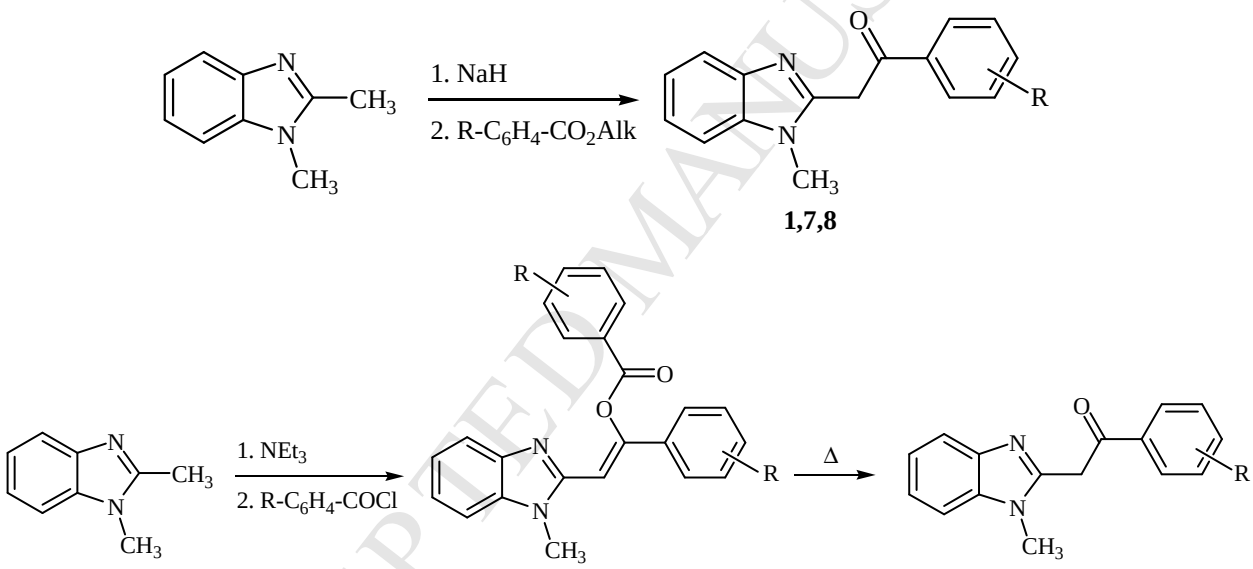
Geometries for the isolated molecules (vacuum) of the tautomers were optimized using the second order Möller-Plesset method (MP2) [24,25]. Computations were carried out utilizing the split-valence triple-zeta basis sets 6-311+G(d,p) [26]. The chemical shifts of carbon and hydrogen atoms (relative to TMS, ppm) were evaluated by gauge invariant atomic

orbitals (GIAO) method at the B3LYP/ cc-pVTZ level of theory by using the PCM model [27]. All calculations were performed with use of Gaussian 09 package [28].

The figure of molecules was prepared with Dassault Systèmes BIOVIA, Discovery Studio Modeling Environment [29].

Results and Discussion

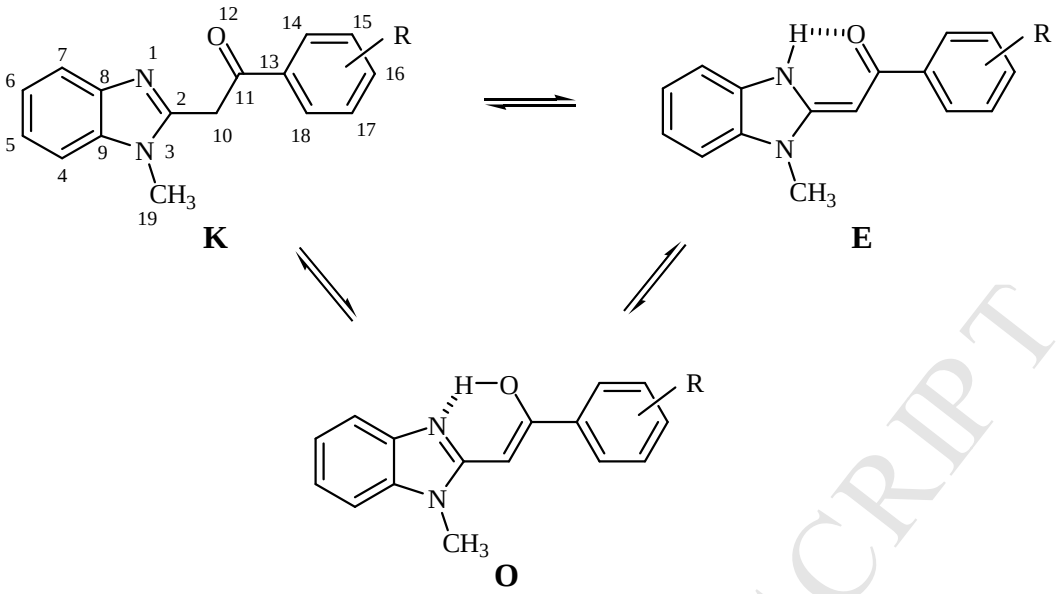
1-methyl-2-phenacylbenzimidazoles were earlier prepared by at least two different methods [9-12,30]. 1,2-dimethylbenzimidazole and substituted alkyl benzoates or benzoyl chlorides were used as substrates in the present paper (Scheme 2). Moreover, usage of the base (sodium hydride or triethylamine) was necessary to abstract proton from the 2-methyl group (this step was then followed by benzoylation).



R = *p*-N(CH$_3$)$_2$ (**1**), *p*-OCH$_3$ (**2**), *p*-CH$_3$ (**3**), *m*-CH$_3$ (**4**), H (**5**), *p*-Br (**6**), *m*-Cl (**7**), *p*-NO$_2$ (**8**)

Scheme 2. Synthesis of 1-methyl-2-phenacylbenzimidazoles

The ketimine form, **K**, of 1-methyl-2-phenacylbenzimidazoles (Scheme 3) was expected to tautomerize into enolimine, (*Z*)-2-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)-1-phenylethenol (**O**) and enaminone, (*E*)-2-(1-methyl-1*H*-benzo[*d*]imidazol-2(*3H*)-ylidene)-1-phenylethanone (**E**). Both **O** and **E** tautomers included in Scheme 3 are stabilized by intramolecular hydrogen bonds.



Scheme 3. Tautomeric equilibria of 1-methyl-2-phenacylbenzimidazoles

Two different tautomers are often found to be formed during recrystallization (Table 1). According to Huang and Wang these species can be separated by fractional crystallization. The **K** (ketimine) and **O** (enolimine, misnamed as **E**, *i.e.* enaminone) appear as colourless and pale yellow crystals, respectively. Based on IR spectral data (KBr tablets), it was observed that these species differ from each other as follows: 1630 cm^{-1} (C=O) for **O** and *ca* 1670 cm^{-1} (C=O) for **K**. On the other hand, only the **K** form was obtained during recrystallization of the *p*-methoxy derivative [9,10]. Our studies of the same derivative, which were performed in the solid state by using ^{13}C CPMAS NMR, revealed that *p*-methoxy-substituted ketimine tautomer (compound **2**) is the only present form in the crystalline state. On contrary to the ^{13}C CPMAS NMR spectra for compound **8** (with the *p*-nitro substituent), which show only enolimine form (Table 2).

Table 1. Overall reaction yields (with respect to 1,2-dimethylbenzimidazole) and melting points of compounds **1**-**8**

Compound	Yield (%)	mp (ºC)	Products characteristics
1	36	228-230	yellow prisms
2	45	139-142 135-136[e] [9-10]	white needles

3	35	101-104 and 154-156 131-132[a] and 122-123[b] [9]	yellow prisms
4	24	109-110	yellow prisms
5	40	119-121[c] and 149-152[d] 150-151[a] and 134-134.5[b] [9] 150-152 [11,12], 150.0-151.5 [14,30]	pale yellow prisms and colorless needles
6	83	120-123 and 157-158	greenish needles
7	57	135-137	yellow prisms
8	80	207-210	orange needles

[a,b] Mp's of different tautomeric forms (see Discussion).

[c] Plates.

[d] Needles.

[e] Mp of the **K** tautomeric form [9,10].

Values of C11 chemical shift reveal that not only **K** tautomer is present in $CDCl_3$ solution but also **O** tautomer [31]. The downfield signal of the acidic protons confirms that the enolimine tautomer is therefore present in solution [13]. During our studies, OH protons were observed at *ca* 13 ppm in chloroform, while the resonance at *ca* 12 ppm in $CDCl_3$ was assigned to the **O** form (enolimine, misnamed as E, *i.e.* eneminone) by Huang et al. [9,10] and ca 14 ppm in DMSO-d_6 by Dzvinchuk [14].

Table 2. Selected calculated (italic) (B3LYP/cc-pVTZ) and experimental ^{1}H and ^{13}C NMR chemical shifts for 1-methyl-2-phenacylbenzimidazoles and their tautomers (solutions in $CDCl_3$)

Tautomer	H10	C2	C10	C11	H19	C19	O–H
1K	4.65	149.40	37.95	190.66	3.75	30.85	
1O	5.75	153.99	77.22	a	a	a	a
2K	4.83	148.56	37.94	191.38	3.86	30.94	
	4.44	*156.93*	*46.00*	*201.96*	*3.94*	*32.46*	
		145.74[b]	42.26[b]	196.06[b]		31.18[b]	

2O	5.83	154.57	75.65	174.96	3.66	29.12	a
	6.32	*162.89*	*84.86*	*173.21*	*3.76*	*30.67*	*14.53*
3K	5.02	148.42	37.91	192.21	3.80	31.95	
3O	5.82	154.47	76.57	174.83	3.61	29.15	a
4K	4.72	148.8	39.02	194.16	3.75	30.40	
4O	5.89	154.39	77.2	174.38	3.66	29.08	13.74[c]
5K	4.95	148.27	38.17	192.54	3.83	30.88	
	4.60	*157.03*	*46.11*	*204.16*	*4.03*	*32.65*	
5O	5.91	154.41	76.94	174.82	3.68	29.16	13.83[c]
	6.49	*162.45*	*86.41*	*173.59*	*3.80*	*30.77*	*14.58*
6K	4.81	148.10	38.68	192.73	3.78	31.87	
6O	5.82	154.10	76.15	174.70	3.64	29.06	13.19[c]
7K	5.34	143.7	37.92	191.27	3.91	31.92	
7O	5.84	154.14	76.25	175.01	6.69	29.18	a
8K	4.73	148.42	a	190.88	a	31.95	
	4.59	*155.60*	*46.49*	*204.02*	*3.89*	*32.53*	
8O	5.59	153.82	77.45	174.17	3.75	29.30	13.36[c]
	6.68	*161.10*	*91.29*	*169.92*	*3.84*	*31.03*	*14.69*
		147.93[b]	87.29[b]	164.46[b]		31.96	

[a] Signal not observed.

[b] The respective ^{13}C CPMAS chemical shifts.

[c] Very broad signal.

Content of the ketimine form in chloroform solutions of 1-methyl-2-phenacylbenz-imidazoles can be found in Table 3 (it is based on integrals of the H10 and H19 signals). π-electron delocalization was found to be the main reason responsible for the tautomeric preferences of 2-phenacylpyridines [16] (other effects such as strength of the intramolecular hydrogen bond should also be taken into account). Other numerous phenacyl derivatives can be also sufficiently stabilized by the electron-donor substituent (Scheme 4). Unfortunately, the linear correlations of amount of the tautomer with the substituent constants [32] are of rather low quality (linear correlation coefficient ≤ 0.8).

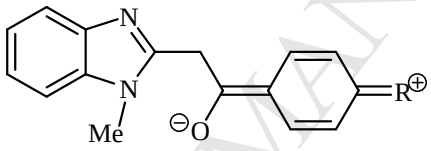
Table 3. Content of the **K** form (%) in $CDCl_3$ solutions

	K[a]	**K**[b]
1	100	83
2	65	65
3	63	64
4	29	29
5	32	33
6	14	14
7	c	c
8	4	0

[a] Based on integrals of the H10 signals.

[b] Based on integrals of the H19 signals.

[c] Unrecurring data.



Scheme 4. Stabilization of the ketimine form by electron-donor substituent

Quantum-chemical calculations

In our work, obtained experimental data were compared with the results of the quantum-chemical calculations. The MP2 procedure is recommended as the most accurate and effective *ab initio* method for studying the medium size molecules involving hydrogen bonds [33]. It includes electron correlation, so the calculated and experimental data are expected to be comparable [34]. Some optimized bond lengths and dihedral angles in the molecules of 1-methyl-2-phenacylbenzimidazoles and their tautomers are presented in Table 4, where hydrogen bond is shorter in the enolimine form than in the enaminone form. Additionally, hydrogen bond angles and the distances between atoms N1 and O2 are greater in the **O** tautomer than **E** tautomer. Therefore, based on the geometry of hydrogen bond [35,36], it can be concluded that the enolimine form is more stable than enaminone form.

It can be stated that the substituent only slightly affects the conformation of each tautomer (Table 4). The carbonyl group is twisted with respect to the neighbouring benzene ring by ca 30° (in general, this twist is independent on tautomer). The six-membered pseudo

rings including the intramolecular hydrogen bonds in both enolimines and enaminones are almost planar.

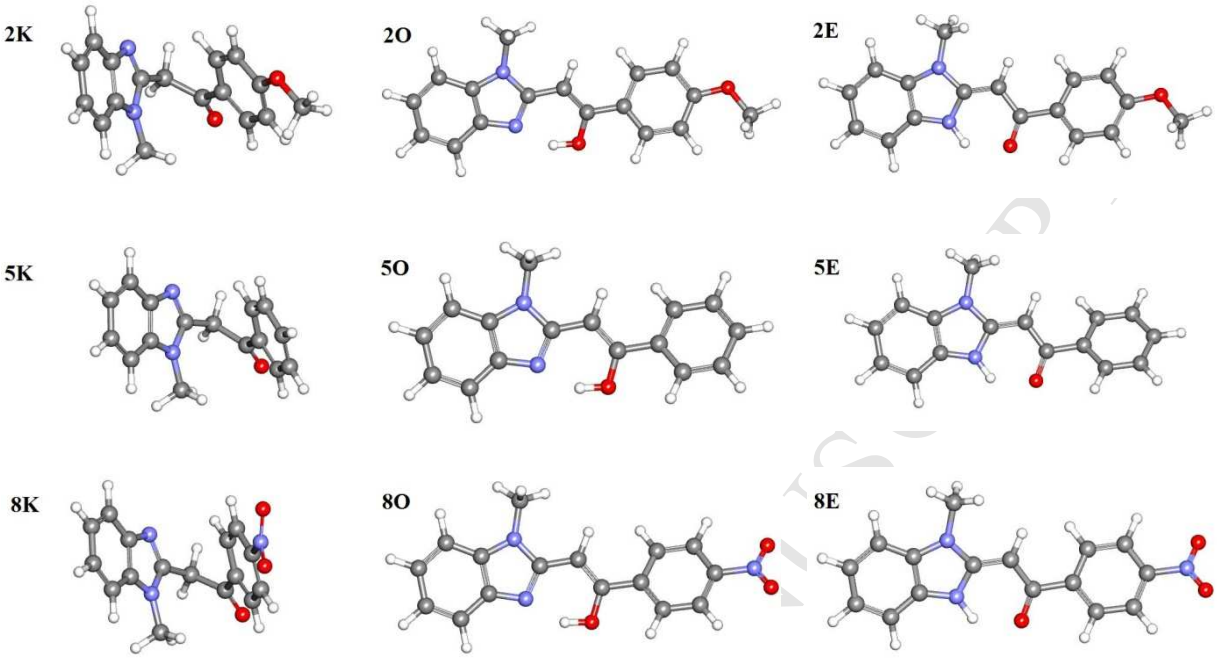


Fig. 1. Optimized structures of selected 1-methyl-2-phenacylbenzimidazoles

Table 4. Selected calculated (MP2/6-311+(d,p) bond lenghts [Å], distances between atoms [Å] and interplanar angles [deg] in 1-methyl-2-phenacylbenzimidazoles and their tautomers

	O12–H12 (in **O**) or N1–H1 (in **E**)	N1···H12 (in **O**) or O12···H1 (in **E**)	N1···O12	N1H12O12	C14C13C11O12 C18C13C11O12
2K	-	-	-	-	-22.87
2O	0.99	1.71	2.62	148.89	-28.35
2E	1.03	1.82	2.60	129.74	-29.39
5K	-	-	-	-	-24.72
5O	0.99	1.72	2.62	148.79	-31.62
5E	1.03	1.82	2.60	129.84	-31.62
8K	-	-	-	-	-284.98
8O	0.99	1.71	2.62	148.81	-28.35
8E	1.03	1.82	2.60	129.84	-30.02

The calculated energies of different tautomers (Table 5) show that the **K** form is the most stable (both electron-donor and electron-acceptor substituents follow this rule). The **O**

Table 5. MP2(6-311+G(d,p) calculated relative energies [kJ mole^{-1}] of different tautomers

2K	0.00[a]
2O	12.55
2E	33.47
5K	0.00[b]
5O	12.55
5E	33.47
8K	0.00[c]
8O	8.37
8E	25.10

[a] Absolute energy: -915.0265 Hartree.

[b] Absolute energy: -800.7661 Hartree.

[c] Absolute energy: -1004.8717 Hartree.

form is always less stable than ketimine (the more electronacceptor is the substituent, the more stable is the enolimine form). Thus, the order of stability of these two tautomers is reversed with respect to 2-phenacylbenzoxazoles [13]. In spite of the fact that both **E** and **O** are stabilized by rather strong [37-40] intramolecular hydrogen bonds, only **E** tautomer is unstable (both electron-donor and electron-acceptor substituents follow the rule). It is noteworthy that in molecule of enolimine tautomer, benzen is aromatic and pseudo ring with hydrogen bond is quasi-aromatic, while imidazole ring probably is aromatic; on the other hand, in the enaminone molecule, it is only the case for benzene and pseudo ring (Scheme 3). Therefore, **O** seems to be more stable than **E**.

Conclusions

Indicated aims were achieved through the synthesis of a series of substituted derivatives of 1-methyl-2-phenacylbenzimidazoles. Tautomeric forms were identified on the

basis of magnetic nuclear resonance spectra of ^{1}H and ^{13}C isotopes. 1-methyl-2-phenacylbenzimidazoles (ketimine, **K**) were found to be in equilibrium in chloroform solutions with their enolimine tautomeric forms, *i.e.*, 2-(1-methyl-1*H*-benzo[*d*]imidazol-2yl)-1-phenylethenols (**O**). No 2-(1-methyl-1*H*-benzo[*d*]imidazol-2(3*H*)-ylidene-1-phenyl-ethanones (enaminone tautomer, **E**) were detected. Therefore, content of the ketimine form strongly depends on substituent, where electron-donor groups present in the molecule stabilize this form. The obtained experimental data were compared with the results of the quantum-chemical calculations. The MP2 calculated energies support the observed tautomeric preferences (both electron-donor and electron-acceptor substituents follow the rule). Although, both **O** and **E** tautomers are stabilized by intramolecular hydrogen bonds, the geometry of hydrogen bond indicates that the enolimine form is more stable than enaminone form. Thus, the most labile tautomer is always enaminone.

Conflict of interest

The authors confirm that this article's content has no conflicts of interest.

Acknowledgments

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Highlights

- Synthesis of 1-metyhyl-2phenacylbenzimidazoles are presented
- Compounds are characterized using NMR and quantum-chemical calculations
- 1-Methyl-2-phenacylbenzimidazoles (ketimine) are in chloroform solutions in equilibrium with their enolimine form
- Type of the substituents plays a significant role in tautomeric equilibrium