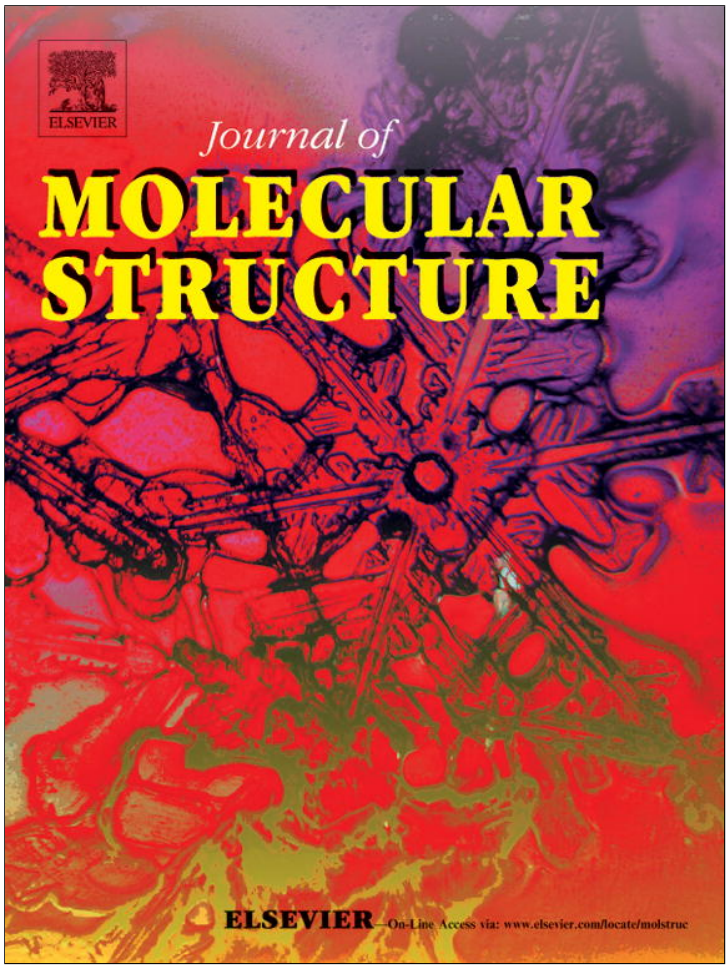

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The structures and stabilities of biologically active 1-phenacyl- and 1-benzoylethyl-derivatives of the pyridinium cation

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ABSTRACT

Chlorides of 1-phenacylpyridinium (**1**), 2-methyl-1-phenacylpyridinium (**2**), 1-benzoylethylpyridinium (**3**) and 1-benzoylethylpyridinium-4-aldoxime (**4**) were synthesized and characterized by X-ray diffraction and by electronic absorption and NMR spectroscopies. Although declared as pharmacologically active in extracellular fluids, their stability and ionization ability as well as predominant ionic forms in aqueous environments were not clarified. Comparative electronic absorption spectral studies in aqueous media at 25 °C and I = 0.1 M performed in this work revealed the predominance of their keto-tautomeric forms and pronounced differences in stability and ionization ability. The ionization of 1-phenacylpyridinium ions **1** and **2** with pK_a values of 11.57 ± 0.04 and 11.66 ± 0.05, respectively produced enolates (*i.e.*, ylides), while the subsequent base-catalyzed first-order decomposition occurred *via* hydrate zwitterion and produced the benzoate ion and the corresponding 1-methylpyridinium derivative. A different proximate cause of the ascertained instabilities of the 1-benzoylethylpyridinium compounds (**3** and **4**) was determined. The base-catalyzed establishment of the ketone to *gem*-diol equilibrium of **3** was found to have a hydration constant smaller than 0.01. Compound **4** underwent a base-catalyzed breakdown due to the instability of its enolate form which resulted in the formation of a pyridine-4-aldoxime and phenyl vinyl ketone. Ionization constants of **3** and **4** keto-forms were estimated as the lowest possible pK_a values of 12, while the pK_a value of pyridinium aldoxime group of **4** was found to be 8.51 ± 0.04. The identified stabilities and ionization abilities of these compounds were additionally supported by their presented coordination ability toward the iron(II) in the pentacyanoferrate(II) moiety.

1. Introduction

The 1-phenacyl- and 1-benzoylethyl-derivatives of the pyridinium cation represent interesting groups of organic compounds that are susceptible to keto–enol tautomerism and to nucleophilic addition reactions such as hydration in aqueous media. The α-proton abstraction from a —CH_2 —group adjacent to a carbonyl group results in the formation of the respective enolates. Such ionization of the 1-phenacylpyridinium derivatives leads to the formation of reactive pyridinium ylides. A number of 1-phenacylpyridinium halides have received great deal of attention with regards to their stabilities, ionization abilities and structures as well as useful reagents in organic synthetic reactions [1–6]. Such carbonyl-stabilized pyridinium ylides are of special interest as intermediates in different catalytic reactions of the coenzyme pyridoxal (vitamin B6). Significant differences in the predominant tautomeric forms of the 1-phenacylpyridinium derivatives relative to the 2-, 3- and 4-isomers have previously been found and have been attributed to the extent of the enol resonance stabilization [4,5,7]. The derivatives of the 1-benzoylethylpyridinium type, as a higher homologs, have not been systematically studied. The study of the oxime derivatives of 1-phenacylpyridinium and 1-benzoylethylpyridinum cations as a class of pyridinium oximes is of great importance because of their distinct and versatile bioactivities which are closely related to their chelating ability [8,9]. Many oximes, particularly those of the mono- and bis-pyridinium type, are capable of reactivating, both *in vitro* and *in vivo* the human blood acetylcholinesterase (AChE, E.C.3.1.1.7) that has been inhibited by organophosphorus compounds (*e.g.*, pesticides, chemical warfare nerve agents, or drugs used to treat cholinergic disorders) and appear to have other multiple pharmacological activities [10]. Some oximes are currently being used in routine human therapy as antidotes against organophosphate poisons. Additionally, 1-phenacyl- and 1-benzoylethyl-derivatives of pyridinium chloride act as protectors of AChE because of their capability to reversibly inhibit the enzyme [11]. Apparently, they are also effective antidotes in soman poisoning which is associated with the reactivation or protection of AChE [12]. These compounds have been studied in our laboratory to some extent with a view to establish their reactivity

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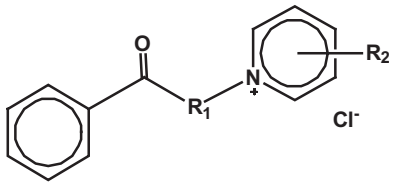
Table 1
The examined pyridinium chloride derivatives.



No.	Name	Abbr.	R_1	R_2
1	1-Phenacylpyridinium chloride	FP-Cl	$-CH_2-$	–
2	2-Methyl-1-phenacylpyridinium chloride	FPM2-Cl	$-CH_2-$	$-CH_3$
3	1-Benzoylethylpyridinium chloride	BEP-Cl	$-CH_2CH_2-$	–
4	1-Benzoylethylpyridinium-4-aldoxime chloride	BEPA4-Cl	$-CH_2CH_2-$	$-HC{=}N-OH$

towards the aquapentacyanoferrate(II) ion, $[Fe(CN)_5(H_2O)]^{3-}$ [13–17]. In attempt to correlate their biological activities, structures and coordinating behavior toward the $[Fe(CN)_5]^{3-}$ moiety, further examinations of their stabilities and ionization abilities in aqueous solutions have been found to be necessary.

In this paper, a detailed structural characterization of the synthesized biologically active carbonyl derivatives of pyridinium and pyridinium-4-aldoxime chloride, as shown in Table 1, was performed using electronic absorption spectroscopy, X-ray diffraction (compounds **1**, **3** and **4**) and NMR (^1H and ^{13}C) spectroscopy. The corresponding ionization constants and predominance of the ionic forms found in aqueous solutions at different pH values were determined. Their newly found short-term stability was related to their enolization tendency as well as hydration effect. Additionally, an unexpected difference in transformation of 1-benzoylethylpyridinium cations (**3** and **4)** in aqueous environments was detected and verified.

2. Experimental

2.1. Materials

The starting materials for the synthesis of **1**–**4** were reagent grade Aldrich products that were employed as purchased. Compounds **1**–**3** were synthesized according to a general procedure by mixing ethanol solutions of the corresponding pyridine compound, which was present in a threefold excess with 2-chloroacetophenone and 3-chloropropiophenone. Compound **4** was obtained by mixing an equimolar ethanol solution of pyridine-4-aldoxime and 3-chloropropiophenone. Pure colorless crystals of the monohydrate salt of **1** and the anhydrous salts of **3** and **4** were obtained by recrystallization from ethanol with the controlled addition of diethylether. The constant pH values of the aqueous solutions were maintained by using Britton and Robinson buffers [18]. The solutions of **4** were also prepared by using a citrate and glycine buffer system (pH = 8.00). Sodium amminepentacyanoferrate(II), $Na_3[Fe(CN)_5(NH_3)]\cdot 3H_2O$ (Sigma–Aldrich), was recrystallized from a concentrated ammonia solution. Solutions of $[Fe(CN)_5(H_2O)]^{3-}$ were obtained by aquation of $[Fe(CN)_5(NH_3)]^{3-}$. They were freshly prepared at room temperature and stored in the dark to minimize photolytic and thermal decomposition. The acetonitrile and acetophenone were of spectrophotometric reagent-grade (Sigma–Aldrich; ≥99.5%).

2.2. Instruments

The FT-IR and FT-Raman spectra were recorded on a Perkin Elmer Spectrum GX, Series R spectrometer in the range of 4000–400 cm^{-1} using KBr pellets. The ^1H- and ^{13}C-NMR spectra were recorded at room temperature on a Bruker Avance 600 spectrometer operating at 600.133 MHz for the ^1H nuclei or 150.917 MHz for the ^{13}C nuclei. The spectra were recorded in DMSO-d_6. TMS was used as the internal standard. The mass spectra were recorded on an Extrel FTMS 2001-DD spectrometer using the direct laser desorption/ionization technique. A summary of the analytical spectral data is presented in Table 2. The single crystal X-ray diffraction data were collected on an Oxford Diffraction Xcalibur 3 CCD diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). The electronic absorption spectral measurements were performed at 25 °C on a UNICAM UV 4 and/or Varian Cary Bio 100 spectrophotometer with thermostated cell holders and 1-cm silica-glass cells. All the pH measurements were performed at 25 °C on a Mettler Toledo pH meter with an InLab 413 electrode accurate to ±0.01 pH units.

2.3. Electronic absorption spectral studies and determination of the ionization constants

The electronic absorption spectra of the examined compounds were acquired in either buffered aqueous solutions, 0.01 M NaOH or acetonitrile (a nonhydroxylic solvent) and compared with the spectrum of the immanent chromophores in 1-phenacylpyridinium-4-aldoxime chloride (**FEPA4-Cl**) and **4**, which are acetophenone and pyridinium-4-aldoxime chloride. Time-dependent electronic absorption spectra studies have shown that the specific aqueous solutions of the examined compounds are not stable regardless of the type of the buffer used. For the ionization studies, therefore, the absorption measurements were performed immediately after the solutions were prepared. Under such conditions the plots of the maximal absorbances as a function of pH were consistent with a clean acid–base equilibration and the pK_a values were evaluated from the absorbance *vs.* pH data by the general method of Albert and Serjeant [19]. The pK_a values were computed by fitting the measured absorbances (A) at a given wavelength as a function of pH to Eq. (1), where A_{HnB} and $A_{H(n-1)B}$ are the absorbances of the acid and the conjugate base forms respectively (n = 1 or 2, with the charge of the ionic species omitted). The parameters A_{HnB}, $A_{H(n-1)B}$ and K_a were evaluated by fitting a non-linear curve to Eq. (1) using the Levenberg–Marquardt algorithm.

$$A = \frac{A_{H_nB}\cdot[H^+]^n + A_{H_{n-1}B}\cdot K_{a1} + (n-1)\cdot A_{H_{n-2}B}\cdot K_{a1}\cdot K_{a2}}{[H^+]^n + K_{a1}\cdot[H^+]^{n-1} + (n-1)\cdot K_{a1}\cdot K_{a2}} \quad (1)$$

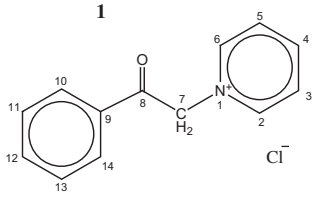
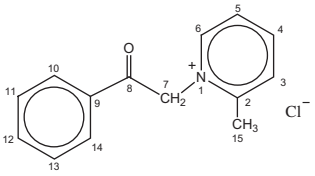
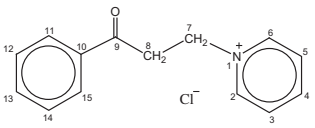
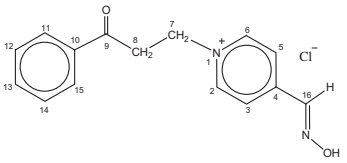
2.4. Kinetic measurements and NMR studies

All of the reactions were followed spectrophotometrically at 25.0 ± 0.1 °C using a Varian Cary Bio 100 spectrophotometer. The decomposition rates of **1**, **2** and **FEPA4-Cl** in 0.01 M NaOH as well as the rates of hydration of **3** and the decomposition of **4** in water and buffered solutions were determined by monitoring the decrease in absorbance at 400, 390, 440, 252 and 340 nm, respectively. The reactions followed first-order kinetics for more than five half-lives and the rate constants were calculated by fitting the data to the exponential form of the first-order rate equation. In all of the kinetic solutions, the ionic strength was maintained at 0.1 M by the presence of an appropriate concentration of NaCl.

To determine the ketone/*gem*-diol ratio, the D_2O solution of **3** was examined using ^1H-NMR spectrometry. The 0.03 M solution of **3** was allowed to equilibrate for 2 days at room temperature before recording the ^1H-NMR spectrum.

The decomposition products of **4** in buffered aqueous solution at pH = 8.6 were examined by ^1H- and ^{13}C-NMR spectrometry. The 0.01 M solution of **4** was prepared and left at room

Table 2
A summary of the analytical spectral data of the prepared compounds **1**–**4**.

	1		**2**		**3**		**4**	
								
	NMR analysis. the proton and carbon chemical shifts (ppm)							
Atom	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C
1	–	–	–	–	–	–	–	–
2	9.21	146.43	–	156.50	9.28	145.58	9.15	145.78
3	8.30	127.87	8.20	129.79	8.18	127.79	8.24	123.77
4	8.76	146.43	8.63	146.37	8.61	145.66	-	148.57
5	8.30	127.87	8.12	125.65	8.18	127.79	8.24	123.77
6	9.21	146.43	9.12	146.91	9.28	145.58	9.15	145.78
7	6.76	66.27	6.74	63.94	5.02	56.22	4.95	55.78
8	–	191.08	–	190.97	4.01	39.11	3.96	38.94
9	–	133.70	–	133.66	–	197.04	–	197.02
10	8.09	128.41	8.13	128.67	–	135.84	–	135.85
11	7.64	129.19	7.67	129.18	7.97	128.08	7.97	128.09
12	7.79	134.74	7.81	134.96	7.55	128.89	7.56	128.92
13	7.64	129.19	7.67	129.18	7.67	133.86	7.68	133.89
14	8.09	128.41	8.13	128.67	7.55	128.89	7.56	128.92
15	–	–	2.51	19.79	7.97	128.08	7.97	128.09
16					–	–	8.43	145.13
OH							12.93	
	The most important experimental FT-IR and Raman frequencies (cm^{-1})							
	IR	Raman	IR	Raman	IR	Raman	IR	Raman
ν (O—H)$_{water}$	3569		3434		3450			
ν (O—H)$_{oxime}$	–	–	–	–	–	–	3351	
ν (C=O)$_{aromatic\ ketone}$	1692	1696	1694	1701	1676	1675	1687	1688
δ (H$_2$O)$_{water}$	1636	1642	1621	1630	1629	1636		
ν (C=N)$_{oxime}$	–	–	–	–	–	–	1645	1647
	1594	1600	1596	1600	1595	1600	1602	1608
ν (CC, CN)$_{aromatic}$	1578	1581	1580	1580	1577	1581	1580	1580
							1520	1523
	1493	1507	1492	1497	1488		1474	
ν (N—O)$_{oxime}$	–	–	–	–	–	–	994	1005
				FTMS analysis				
[M—Cl]$^{+}$	Calculated	Observed	Calculated	Observed	Calculated	Observed	Calculated	Observed
m/*z*	198.09134	198.092723	212.106990	212.108858	212.106990	212.104096	255.112804	255.111514

temperature for 5 h. Following the removal of water by lyophilization, solid mixture was dissolved in DMSO-d_6 and its NMR spectra recorded. The interpretations of the obtained spectra were based on the comparison with the spectra of **4**, phenyl vinyl ketone [20] and pyridine-4-aldoxime.

2.5. X-ray crystallographic study

The diffraction data of **1·H₂O**, **3**, and **4** (see Table S1 in Supplementary data) were reduced using the CrysAlis software package [21]. The solution, refinement and analysis of the structures were performed using the integrated software in the WinGX system [22]. The structures were solved by direct methods (SHELXS) and refined by the full-matrix least-squares method based on F2 against all reflections (SHELXL-97) [23]. The non-hydrogen atoms were refined anisotropically. All of the hydrogen atoms were located in the difference Fourier maps. The hydrogen atoms of a water molecule in **1·H₂O** were refined using restraints on the bond lengths (DFIX 0.89 0.01) and angles (DANG 1.42 0.02). The rotating group refinement procedure (AFIX 147) was used for the hydroxyl hydrogen atom in **4** whereas the carbon-bonded hydrogen atoms were refined using the riding model (AFIX 23 and AFIX 43). Geometrical calculations were performed using PLATON [24] and the figures were constructed using ORTEP-3 [25] and MERCURY [26]. The parameters in the CIF form are available as Electronic Supplementary information from the Cambridge Crystallographic Data base Centre (CCDC 775732).

3. Results and discussion

3.1. The crystal structures of 1·H₂O, 3, and 4

Compound **1** was crystallized as a monohydrate whereas **3** and **4** were obtained as crystals of the anhydrous salts. The crystallographic asymmetric units of the reported structures are depicted in Fig. 1. A search of the Cambridge Structural Database (CSD; Version 5.31, with August 2011 updates) [27] revealed no entries containing the 1-benzoylethylpyridinium moiety. Therefore, the molecular geometries of **3** and **4** were compared with those of the related 1-phenacylpyridinium derivatives. The selected bond lengths and angles of **1·H₂O**, **3**, and **4** (Table 3) were similar to those found in the structures containing the 1-phenacylpyridinium moiety [2c,13,28]. The N1—C7 bond was significantly shorter in **1·H₂O** than in the 1-benzoylethylpyridinium derivatives **3** and **4**. A considerable quinoidal character of the pyridinium ring (manifested by the C2—C3 and C5—C6 bonds being significantly shorter than the C3—C4 and C4—C5 bonds) was observed for **4**. The quinoidal character in **3** was less pronounced and the pyridinium ring in **1·H₂O** possessed no quinoidal character at all. The aldoxime group in **4** was in the *E*-configuration and should be noted that the same

Table 3
Selected bond lengths (Å) and angles (°) for **1·H₂O**, **3** and **4**.

	1·H₂O[a]	**3**[b]	**4**[b]
O1—C*n*	1.217(2)	1.2199(19)	1.220(4)
N1—C2	1.344(2)	1.3535(18)	1.360(3)
N1—C6	1.341(3)	1.343(2)	1.356(3)
N1—C7	1.466(2)	1.480(2)	1.481(3)
C2—C3	1.376(3)	1.366(2)	1.357(4)
C3—C4	1.366(3)	1.378(2)	1.406(4)
C4—C5	1.365(3)	1.384(2)	1.405(4)
C5—C6	1.359(3)	1.364(2)	1.369(4)
C(*n* − 1)—C*n*	1.499(2)	1.503(2)	1.500(4)
C*n*—C(*n* + 1)	1.481(2)	1.489(2)	1.505(4)
O2—N2			1.387(3)
N2—C16			1.282(3)
C4—C16			1.452(4)
C2—N1—C6	120.94(15)	120.34(13)	120.1(2)
N1—C7—C8	112.24(14)	111.39(12)	110.1(2)
C(*n* − 1)—C*n*—C(*n* + 1)	116.97(15)	119.14(13)	118.3(3)
O2—N2—C16			112.4(2)
N2—C16—C4			117.0(2)

[a] *n* = 8.
[b] *n* = 9.

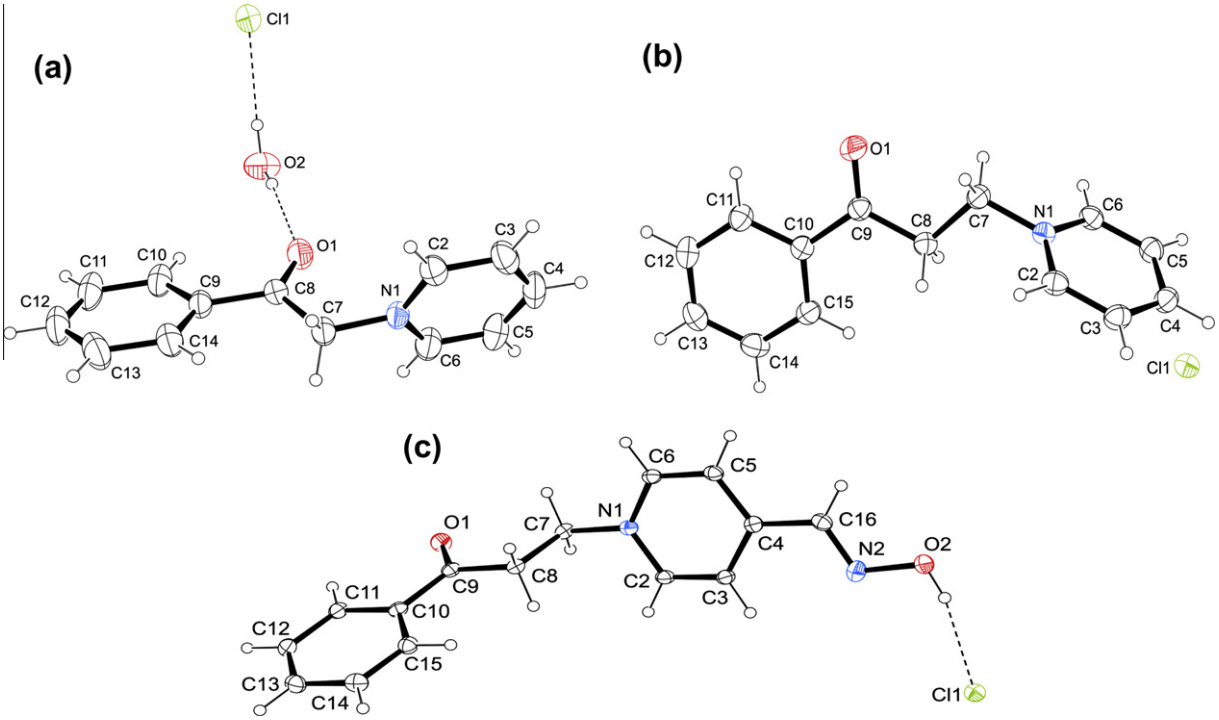


Fig. 1. The asymmetric unit of (a) **1·H₂O**, (b) **3** and (c) **4**. The displacement ellipsoids are drawn at the 50% probability level. The hydrogen bonds are denoted by dashed lines.

configuration is also found in all other structures that contain the pyridinium-4-aldoxime moiety [13,29]. The planes of the two aromatic rings, pyridine and phenyl, were inclined at angles of 67.55(11)°, 73.36(8)°, and 59.18(4)° in **1·H$_2$O**, **3**, and **4**, respectively. Each water molecule in the **1·H$_2$O** structure was a hydrogen-bond donor to a 1-phenacylpyridinium cation and a chloride anion (Fig. 1a, see Fig. S1a in Supplementary data). In addition, each 1-phenacylpyridinium cation was connected to another water molecule by a weak C7—H7B···O2 ($1-x$, $1-y$, $1/2+z$) interaction (see Table S2 in Supplementary data). Surprisingly, there were no π···π interactions detected in the **1·H$_2$O** structure. Quite distinctively, the two centrosymmetrically related (symmetry operator: $1-x$, $-y$, $1-z$) pyridine rings in the structure of **3** (Fig. 1b) formed π···π interactions with distances between their centroids of 3.7858(9) Å and a slippage of 1.587(1) Å. There were also weak C—H···π interactions between the ethyl groups and the phenyl rings that linked the two 1-benzoylethylpyridinium cations into a centrosymmetrical dimer (see Fig. S1b and Table S2 in Supplementary data). In the structure of **4**, the aldoxime hydroxyl group was hydrogen bonded to a chloride anion (Fig. 1c). The parallel pyridine and phenyl rings of the neighboring cations were alternately stacked by two kinds of π···π interactions (see Fig. S1c in Supplementary data) with the following geometries: (1) distance between the centroids Cg(phenyl)···Cg(pyridine) [$1-y$, $x-y$, $z-1/3$] of 3.765(2) Å with a slippage of 1.101(2) Å; (2) distance between Cg(phenyl)···Cg(pyridine) [$1-y$, $1+x-y$, $z-1/3$] of 3.825(2) Å with a slippage of 1.575(2) Å. In all three reported structures, the chloride anions formed C—H···Cl contacts with the surrounding cations (see Table S2 in Supplementary data).

3.2. Spectral studies of stabilities and ionization abilities in aqueous solutions

The electronic absorption spectra of compounds **1**–**4** in aqueous solutions generally exhibited the pH-dependent bands that were compatible with the absorptions of the inherent chromophores. The time-dependent spectrophotometric studies showed considerable differences in the stabilities and ionization abilities of the 1-phenacyl (**1**, **2** and the recently studied 1-phenacylpyridinium-4-aldoxime chloride, **FEPA4-Cl** [13]) and 1-benzoylethyl- (**3** and **4**) pyridinium derivatives.

The spectra of aqueous solutions of **1** and **2** were composed of an intense band at 250 nm and weaker absorptions in the 270–290 nm range. These composite bands originated from the overlapped $\pi \rightarrow \pi^*$ transitions within the acetophenonic and the pyridinium chromophores. Ionization of the keto-tautomers **1** and **2** and formation of the respective enolates (*i.e.*, ylides), resulted in additional conjugation bands at 400 and 390 nm, respectively (Fig. 2). Solutions of **1** and **2** were stable, provided the exposure to the basic media was not prolonged. The spectra of **1** and **2**, prior to ionization, were analogous to the spectra obtained in acetonitrile, a nonhydroxylic solvent, supporting the expected predominance of their ketone forms. In contrast to earlier spectral interpretation that suggested a considerable fraction of enols in their aqueous solutions [16,17], the predominance of the keto-tautomers of compounds **1**, **2** and **FEPA4-Cl** was in agreement with the poor resonance stabilization of the respective enoles [4,5,7,13].

A base-catalyzed first-order decomposition of the 1-phenacylpyridinium ions (Fig. 3) was observed in alkaline media at pH > 10.0. The bands centered at 250 nm and at 390 and 400 nm for **1** and **2** or at 440 nm for **FEPA4-Cl** progressively disappeared while a new composite band in the 260–270 nm region was produced indicating the formation of the same type of degradation products. Moreover, similar rates of decomposition in the 0.01 M NaOH solution at 25.0 °C were observed. The rates were

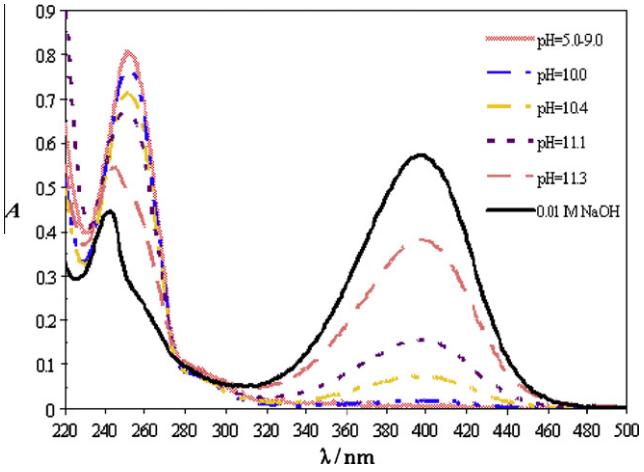


Fig. 2. The pH-dependent spectra of **1** collected immediately after solution preparation at 25 °C, $I = 0.1$ M and $c = 4 \times 10^{-5}$ M.

$k(\mathbf{1}) = 8.9 \times 10^{-4}\ s^{-1}$, $k(\mathbf{2}) = 2.1 \times 10^{-4}\ s^{-1}$ and k(**FEPA4** [13]) = $7.4 \times 10^{-4}\ s^{-1}$ suggesting the same mechanism of decomposition.

The final electronic absorption spectra were identical to the spectra of equimolar mixtures of benzoate ion and corresponding 1-methylpyridinium derivatives (see Fig. S2 in Supplementary data), confirming that the decompositions occurred quantitatively. The presence of isosbestic points indicated that the stoichiometries of the reactions remained unchanged during the decompositions and that no secondary reactions occurred.

We assumed that the decompositions of **1**, **2** and **FEPA4-Cl** occurred *via* hydrate zwitterions formations as presented in Scheme 1. The identified decomposition products unambiguously supported a hydroxide ion addition to the carbonyl group in alkaline solutions and the subsequent formation of the hydrate zwitterions. Similar ionization properties and decomposition mechanisms were also found for the related 4-substituted 1-phenacylpyridinium cations, aromatic ketones of 4-phenylacetylpyridinium type and 2-acetylpyridinium ion [30–32].

Implementing methylene group into the structure of 1-phenacylpyridinium cations led to the formation of their higher homologs, 1-benzoylethylpyridinium derivatives, which contained isolated acetophenonic and 1-methylpyridinium chromophores. The ^{13}C-NMR resonance signals indicated a reduced electron density on the carbonyl carbon atom of the 1-benzoylethylpyridinium derivatives relative to their 1-phenacyl-homologs. This was manifested as deshielding by about +6 ppm, suggesting that **3** and **4** might be more susceptible to nucleophilic addition reactions *i.e.*, hydration. The concentration of the formed *gem*-diols is usually very low, but has been shown to increase if the carbonyl group is more predisposed to nucleophilic addition [33]. According to the mutual structural similarity of the **3** and **4** they would be expected to have analogous behaviors. However, introducing an aldoxime group resulted in the significantly altered stability and reactivity of **4** in aqueous solutions. Unlike the stable acetonitrile solutions of the 1-benzoylethyl-derivatives **3** and **4** with well-defined electronic absorption spectra, their spectra were time-dependent in pure water and buffered aqueous solutions. Surprisingly, the time-dependent changes exhibited quite opposite trends. Therefore, the spectral characterization of **3** and **4** are presented separately. The spectrum of the freshly prepared buffered solutions of **3** in a pH range of 5–10 contained the acetophenonic conjugation band at ~250 nm, the shoulder at 260 nm that originated from absorption within the 1-methylpyridinium ring and the weaker benzenoid band of acetophenone at ~285 nm. Analogous spectrum was obtained in acetonitrile, confirming the predominance of the

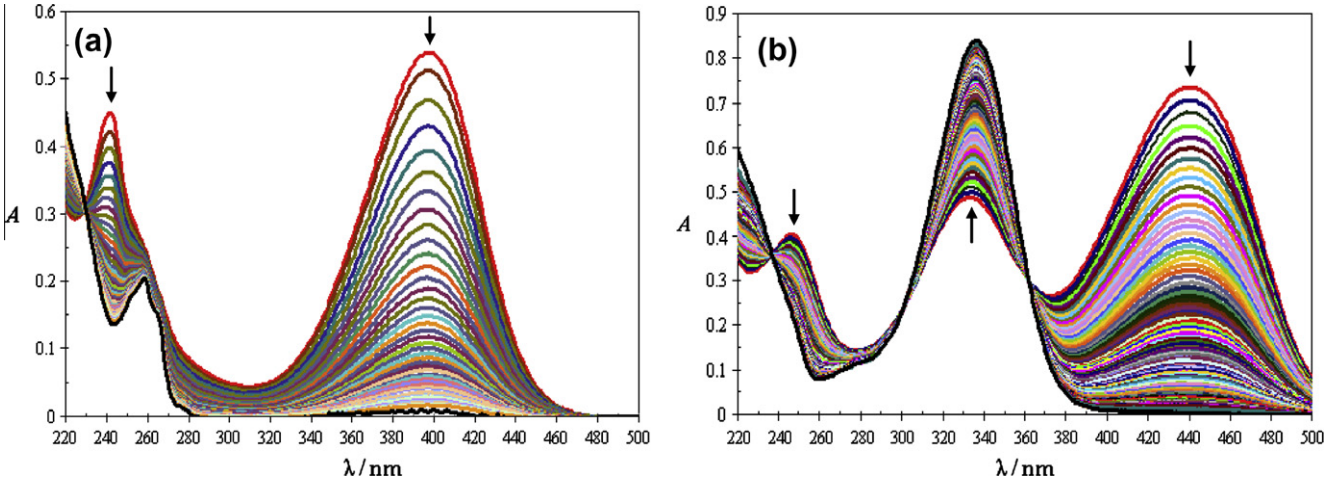
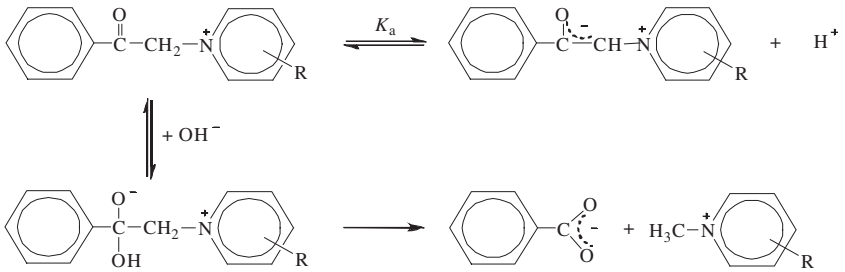


Fig. 3. The time-dependent spectra of (a) **1** and (b) **FEPA4-Cl** in 0.01 M NaOH at 25 °C, $I = 0.1$ M and $c = 4 \times 10^{-5}$ M. The red curve represents the spectrum collected immediately after solution preparation while the black curve indicates the final spectrum. The time intervals were (a) 120 s and (b) 50 s. The black arrows indicate the direction of spectral changes. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)



Scheme 1. Ionization of the 1-phenacylpyridinium ions and their decomposition in alkaline media.

keto-tautomer. A slow spectral change of **3** was observed in pure water, with an apparent rate constant of approximately 1×10^{-6} s^{-1}. The final spectrum was composed of one asymmetric maximum at 257 nm, a shoulder on each side (~251 and 263 nm) and a wide diffuse band in the range centered on 280 nm. Equivalent spectral changes occurred in the buffered solutions (Fig. 4a) with a substantial enhancement of the transformation rate associated with increasing the pH. It seemed likely that the resulting spectral changes were attributable to the equilibration of the carbonyl group in **3** with its hydrated form, the *gem*-diol (Scheme 2). The group of fine structured bands formed in the 250–280 nm region corresponded to the overlap of the benzene absorption from the unconjugated benzene ring in the *gem*-diol, and ketone absorption bands of **3**. Analogous spectra were observed for trifluoroacetophenone after adding water or ethanol to a nonhydroxylic solvent [34]. In the buffered solutions of pH > 10 and in 0.01 M NaOH solution the equilibration was instantaneously manifested as a fine structured spectrum followed by a slow restoration of the spectrum characteristic for the unhydrated keto-tautomer **3** with well-defined isosbestic points at 233 and 252 nm (Fig. 4b).

It was clear that at least two reactions were important in the alkaline media: a fast addition of the hydroxide ion to the carbonyl group producing the hydrate zwitterion; and a slower subsequent reaction that could either be the elimination of the hydroxyl group, resulting in a return to the keto-tautomer **3**, or the reaction with water producing the *gem*-diol and thus causing an equilibrium shift toward the ketone (Scheme 2).

Although the decrease in the absorbance of the acetophenonic band at 250 nm during equilibration in pure water and in buffered solutions (pH = 5–10) seemed to be the appropriate choice for the spectrophotometric estimation of the proportions of hydrate and ketone at equilibrium, the equilibrium was too lopsided to permit determining the hydration constant, K_h. Measuring K_h by ^{1}H-NMR spectroscopy in D_2O (at 25 °C and $I = 0.1$ M) showed that the amount of *gem*-diol was lower than the detection limit indicating a value of approximately 0.01. In contrast to previous findings [17], the absorbance at 250 nm detected immediately after preparation of solution prior to ketone **3**/*gem*-diol equilibration originated exclusively from its keto-form and did not change with the pH, indicating that ionization did not occur.

The spectra of the freshly prepared buffered solutions of **4** in the pH range of 5–7 contained acetophenonic conjugation band at ~250 nm and composite band at 280 nm that originated from the absorption within the 1-methylpyridinium-4-aldoxime ring and the benzenoid absorption of acetophenone. At pH > 7 ionization of the aldoxime group was observed as a new charge transfer band at 340 nm, which is characteristic of the absorption within deprotonated 1-methylpyridinium-4-aldoxime. Compound **4** also exhibited time-dependent changes in the spectra that have been previously recognized around pH = 8 [17] but that also occurred in our experiments with pure water and buffered aqueous pH 5–10 solutions. The spectral changes were manifested as an increase in absorbance at 250 nm that was accompanied by a slight bathochromic shift (~6 nm) and a simultaneous decrease of the band around 280 nm. The ionization of the 1-methylpyridinium-4-aldoxime part of the structure led to the simultaneous decrease in absorbance at 340 nm (Fig. 5). The rate of spectrum transformation with well-defined isosbesticity increased with increasing pH, again demonstrating, a base-catalyzed process. The spectral changes in pure water occurred almost two times faster (apparent

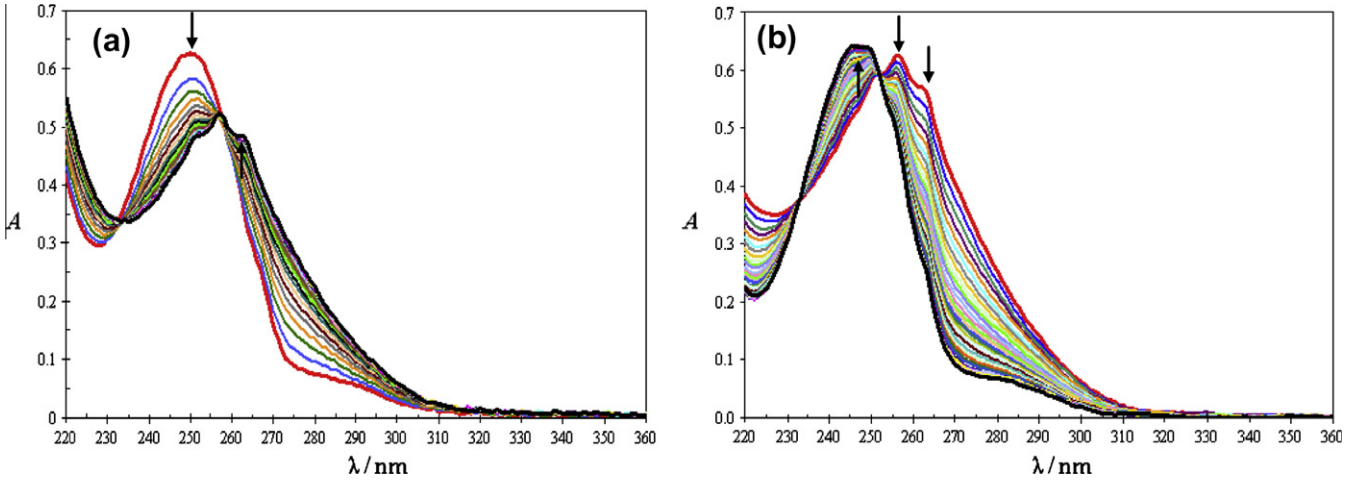
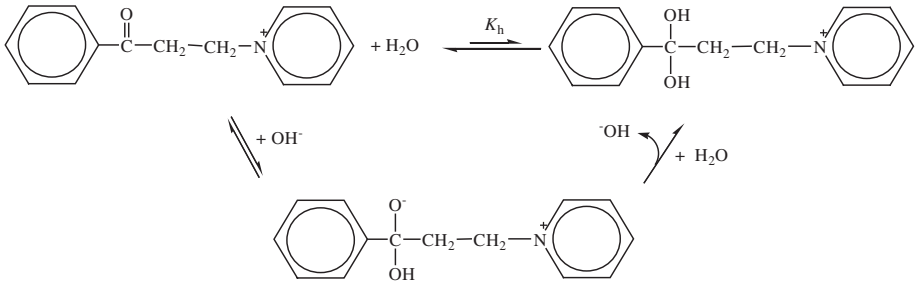


Fig. 4. The time-dependent spectra of **3** in the (a) buffered solution at pH = 8.3 and (b) 0.01 M NaOH, both at 25 °C, I = 0.1 M and $c = 4 \times 10^{-5}$ M. The red curve represents the spectrum collected immediately after solution preparation while the black curve indicates the final spectrum. The time intervals were (a) 120 s and (b) 150 s. The black arrows indicate the direction of spectral changes. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)



Scheme 2. The hydration of the 1-benzoylethylpyridinium cation and its equilibria in the alkaline media.

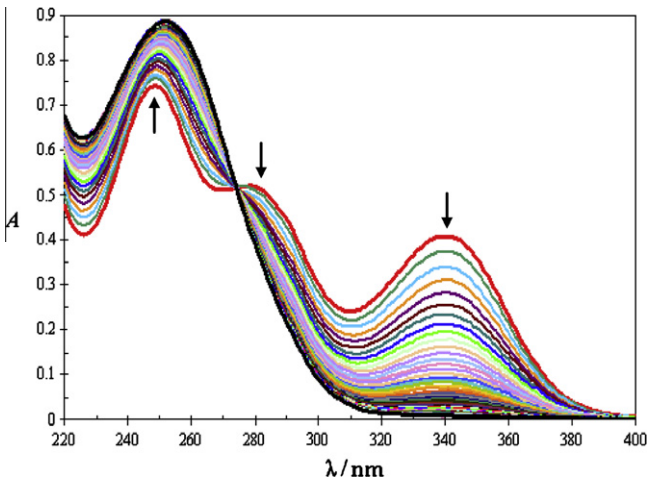


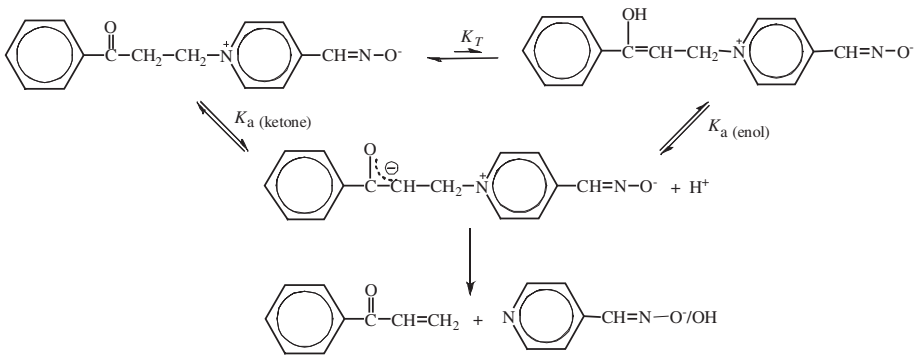
Fig. 5. The time-dependent spectra of **4** in a buffered solution at pH = 8.30, 25 °C, I = 0.1 M and $c = 4 \times 10^{-5}$ M. The red curve represents the spectrum collected immediately after solution preparation while the black curve indicates the final spectrum. The time interval was 60 s. The black arrows indicate the direction of spectral changes.

rate constant approximately 2×10^{-6} s^{-1}) than those of **3** and no restoring of the spectra in the basic media was observed. The final spectrum strongly suggested that the predominant process in the transformation of **4** in aqueous media did not involve the carbonyl group. The breakdown of **4** and the formation of new compounds, one with the preserved acetophenonic part and other with the altered 1-methylpyridinium-4-aldoxime part of the structure were strongly implicated. The final spectrum was associated with the existence of uncharged substituted pyridine chromophore.

The influence of the concentration of **4** on the rate of spectral transformation was investigated by following the rate of disappearance of the maximum at 340 nm (at 25 °C, pH = 8.23 ± 0.02 and I = 0.1 M). The results showed that the reaction was first-order in compound **4** with an observed rate constant of $k_{obs} = (1.5 \pm 0.5) \times 10^{-3}$ s^{-1}. Furthermore, in a pH range of 7–11, the absorbance at 340 nm *vs.* time curves covering at least 95% of the reaction were kinetically first-order in **4** with progressively increasing rate constant regardless to the used buffer system, thus confirming the general base-catalytic effect.

The decomposition products of **4** were identified by NMR analysis of buffered mixture at pH = 8.6. The ^{13}C-NMR signals at 120.46, 140.36, 146.39 and 150.02 ppm as well as ^{1}H-NMR signals at 7.52 (d), 8.16 (s) and 8.59 (d) ppm clearly confirmed the existence of pyridine-4-aldoxime (^{13}C-NMR (DMSO-d_6, δ): 120.77, 140.49, 146.82, 150.31 ppm; ^{1}H-NMR (DMSO-d_6, δ): 7.54 (d), 8.18 (s), 8.60 (d) ppm). The low intensity ^{13}C-NMR signal at 189.99 ppm was in an excellent agreement with the signal of carbonyl group in phenyl vinyl ketone [20], while two doublets at 6.01 and 6.33 ppm as well as the set of singlets in the 7.35–7.44 ppm region observed in the ^{1}H-NMR spectrum confirmed the presence of vinyl group.

Therefore, the decomposition of **4** occurred *via* formation of enolate originating from traces of enol present in tautomeric equilibrium. The following scheme explaining the electronic absorption spectra changes and preliminary kinetic results was proposed (Scheme 3). Further kinetic and mechanistic studies of the decomposition of **4** are in progress.



Scheme 3. The presumed decomposition of the 1-benzoylethylpyridinium-4-aldoxime cation in aqueous media.

3.3. Ionization constants and molar absorption properties

The pH dependence of the absorbance at a fixed-wavelength detected immediately after preparation of the solutions reflected the electronic structures of the keto-tautomers **1**–**4**, described by a clean acid–base equilibration consistent with Eq (1). The relatively slow decomposition of 1-phenacylpyridinium compounds (**1**, **2**) compared with an instantaneous ionization allowed accurate spectrophotometric detection of the enolates (*i.e.*, ylides). The alterations of 1-benzoylethylpyridinium compounds (**3**, **4**) were slow enough and the initial absorbances remained constant within the investigated pH range, substantiating the low ionization ability of the keto-tautomers, with either a protonated or deprotonated 1-methylpyridinium-4-aldoxime part in the case of **4**. The pH dependence of the absorbances at 280 and 340 nm provided an accurate determination of the ionization constant of the 1-methylpyridinium-4-aldoxime part in **4**. The calculated maximal absorbances that were obtained from the kinetic runs were in excellent agreement with those detected in the freshly prepared solutions at pH values from 5 to 10. The pH *vs*. absorbance dependence of the freshly prepared solutions of all the examined compounds is presented in Fig. 6. The evaluated pK_a values along with the maximal molar absorption coefficients of the 1-phenacyl- and 1-benzoylethylpyridinium derivatives in juxtaposition with the similar pyridinium-4-aldoximes, **FEPA4-Cl** and 1-benzylpyridinium-4-aldoxime chloride (**BPA4-Cl**), are listed in Table 4 and compared with the data from the literature. The established higher acidities of the relevant 1-phenacylpyridinium keto-tautomers **1**, **2** and **FEPA4-Cl** relative to their 1-benzoylethylpyridinium homologs **3** and **4** was reasonable, as their enolate forms were much more stable because

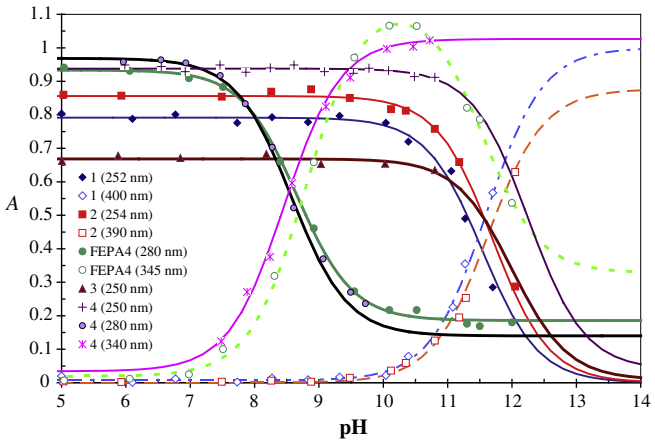


Fig. 6. The pH dependence of the absorbance of freshly prepared solutions of **1**–**4** and **FEPA4-Cl**. The curves represent the non-linear square fit to Eq. (1).

of the possibility of negative charge delocalization in both aromatic rings. The most stable of these compounds was the enolate of **FEPA4-Cl** due to the additional inductive and resonance charge stabilization by the deprotonated aldoxime group. The ionization abilities of the pyridinium-4-aldoxime group in **FEPA4-Cl**, **BPA4-Cl** and **4** were essentially independent of the substituent attached to the 1-methylenepyridinium moiety.

3.4. The $[Fe(CN)_5]^{3-}$ moiety as a selective probe for detection of ligating ionic forms

The pentacyanoferrate(II) moiety is regarded as a selective probe in comparative studies of the iron(II) centre binding capability of specific donor groups in ligands present in several ionic forms. The reactivity and the coordination modes of 1-phenacylpyridinium (**1**, **2**) and 1-benzoylethylpyridinium (**3**, **4**) compounds toward the $[Fe(CN)_5]^{3-}$ moiety were investigated by time-dependent electronic absorption spectral studies in water and buffered pH 5–10 solutions. The results of these studies were in excellent agreement with the variety of the possible ligands' equilibrium ionic forms. Compounds **1** and **2** were found to be nonreactive in the specified solutions, which is consistent with their predominant keto-tautomeric forms that contain a sterically hindered carbonyl group with an oxygen of low basicity. The established differences in the stabilities and ionization abilities of **3** and **4** in the investigated solutions reflect a pronounced difference in their reactivities toward the $[Fe(CN)_5]^{3-}$ moiety. Compound **3** evidently coordinated to the iron through the carbonyl oxygen exhibiting a metal-to-ligand charge transfer band (MLCT) at 365 nm, regardless of the pH of the media. This result additionally confirmed the existence of the reactive ketone **3** as well as the keto/*gem*-diol equilibration as a primary cause of the instability of **3** in the aqueous media. As was shown by the NMR spectroscopy and X-ray diffraction studies, the carbonyl oxygen in **3** and **4** was more basic than in **1** or **2** and therefore was a better σ-donor. The reported kinetics for the complex with **3** in buffered solutions at pH = 8.0 confirmed the formation of the (1-benzoylethylpyridinum)pentacyanoferrate(II) complex [14], although the suggested enolate coordination was mostly based on a wrong assumption about the ionization ability of **3**. The time-dependent electronic absorption spectra of a reaction mixture containing **4** revealed several modes of coordination to the iron centre (see Fig. S3 in Supplementary data). The instantaneous formation of MLCT bands at 338 nm and 580 nm was followed by their disappearance and the formation of a new band at 440 nm which was characteristic of the final complex. The bands at 338 nm and 580 nm indicated a rapid coordination through the carbonyl and aldoxime group, respectively, and the formation of two substituted pentacyanoferrates(II) in the first step. The subsequent formation of the band around 440 nm has been found to be characteristic of the complex produced in the reaction with

Table 4
The ionization constants and molar absorption coefficients of the predominant ionic forms of the examined compounds in aqueous solution at 25 °C, I = 0.1 M and $c = 4 \times 10^{-5}$ M determined immediately after solution preparation.

Comp.	λ_{max} (nm)	$\varepsilon(H_2B)_{max}$ (M^{-1} cm^{-1})	$\varepsilon(HB)_{max}$ (M^{-1} cm^{-1})	$\varepsilon(B)_{max}$ (M^{-1} cm^{-1})	$pK_{a(oxime)}$	$pK_{a(ketone)}$
1	252	–	19790	–	–	11.57 ± 0.04
	400	–	–	25000[a]		10.95 ± 0.06[b]
						10.90[c]
						9.7[d]
2	254	–	21650		–	11.66 ± 0.05
	390	–		21920[a]		>11[b]
FEPA4-Cl	283	23330	–	–	8.72 ± 0.07[e]	11.40 ± 0.20[e]
	345	–	27800	8190	8.34[f]	10.77[f]
	440	–	–	17500[a]		
3	250	–	16690	–	–	≥12.00[a]
						6.67 ± 0.05[b]
4	250	23400			8.51 ± 0.04	≥12.00[a]
	280	24210				
	340		26100	–	9.97 ± 0.04[b]	6.70 ± 0.05[b]
BPA4-Cl	283	–	16194	–	8.76 ± 0.02[e]	–
	342	–	–	24280	8.40[f]	

[a] Estimated values obtained by extrapolation.
[b] Data from Ref. [17]: I = 0.1 M, 25 °C.
[c] Data from Ref. [5]: obtained in dilute NaOH solutions at 25 °C without correction for ionic strength.
[d] Data from Ref. [6]: 25 °C, ionic strength not specified.
[e] Data from Ref. [13].
[f] Data from Ref. [16]: I = 0.1 M, 25 °C.

$[Fe(CN)_5]^{3-}$ and has been used as an analytical wavelength in a previous study of the formation kinetics of **4**-substituted pentacyanoferrate(II) [15]. Unlike earlier assumptions about the participation of the carbonyl group in the coordination, our extended study unambiguously suggests that the predominant reaction involves a coordination of a breakdown product of **4** to the iron(II) centre. In fact, the produced highly reactive pyridine-4-aldoxime (Scheme 3) evidently coordinated *via* the pyridine nitrogen. The energy of the MLCT band of the complex produced and the rate of complex formation strongly supported such findings, as similar MLCT energies have also been found for the substituted pentacyanoferrates(II) with pyridine-type ligands, such as isonicotinamide (435 nm) [35], 4,4′-bipyridine (432 nm) [36] and pyridine-4-aldoxime (435 nm) [37] in which the pyridine nitrogen coordinates to the iron(II).

4. Conclusion

The comparative study of 1-phenacylpyridinium (**1**), 2-methyl-1-phenacylpyridinium (**2**), 1-benzoylethylpyridinium (**3**) and 1-benzoylethylpyridinium-4-aldoxime (**4**) chlorides have been done using electronic absorption and NMR spectroscopies and X-ray diffraction (compounds **1**, **3** and **4**). The time-dependent electronic absorption spectral characterization established the predominance of the keto-tautomeric forms in aqueous solutions. Considerable differences in the stability and ionization ability of the keto-tautomers of 1-phenacyl- (**1**, **2** and **FEPA4-Cl**) and 1-benzoylethyl- (**3**, **4**) pyridinium derivatives in aqueous solutions were found. The 1-phenacylpyridinium derivatives were stable in pure water and in buffered aqueous solutions up to a pH of ~10. Similar pK_a values were found, demonstrating that methyl or aldoxime substitution in the pyridinium ring did not significantly influence the ketone acidity. The base-catalyzed decomposition of **1**, **2** and **FEPA4-Cl** occurred *via* hydrate zwitterion formation, which was clearly supported by the identified products of the decomposition. The keto-tautomers of the 1-benzoylethylpyridinium derivatives (**3**, **4**) exhibited time-dependent electronic absorption spectral changes in pure water and in buffered aqueous solutions. Since no evidence for the formation of the enolates or ylides of **3** or **4** was found in the pH-dependent absorption spectra of the freshly prepared solutions, the low acidity of these ketones ($pK_a \geqslant 12$) were obvious. The instability of **3** in aqueous solutions was due to the hydration of the ketone and the shifts in the ketone/*gem*-diol equilibrium. In the case of **4**, the predominant process included an intramolecular base-catalyzed elimination reaction and the formation of a reactive pyridine-4-aldoxime and phenyl vinyl ketone. The structural properties of these compounds in a solid state and in a solutions were found to be in accordance with the coordination ability toward the iron(II) in the pentacyanoferrate(II) moiety, where the carbonyl group was recognized as a potential σ-donor only in the case of 1-benzoylethylpyridinium derivatives (**3**, **4**).

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.molstruc.2012.03.060.

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