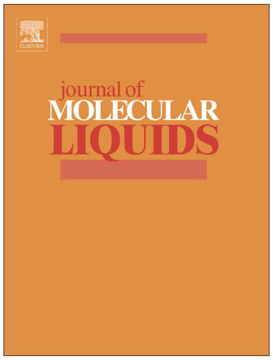

An example of green surfactant systems based on inherently biodegradable IL-derived amphiphilic oximes

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An Example of Green Surfactant Systems Based on Inherently Biodegradable IL-derived Amphiphilic Oximes

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Abstract

Progress in the development of biodegradable ionic liquids (ILs) leads to designing green surfactant formulations for miscellaneous applications. In this work, we present synthesis of a series of novel IL-derived amphiphilic pyridinium oximes composed by octylamide tail linked to the headgroup by means of amide, 4-((hydroxyimino)methyl)-1-(2-(octylamino)-2-oxoethyl)pyridin-1-iumbromide, **4-PyC8**), alanyl ((*S*)-4-((hydroxyimino)methyl)-1-(2-((1-(octylamino)-1-oxopropan-2-yl)amino)-2-oxoethyl) pyridin-1-ium bromide, **4-PyAlaC8**), or phenylalanyl ((*S*)-2-((hydroxyimino)methyl)-1-(2-((1-(octylamino)-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)-pyridin-1-ium bromide, **2-PyPheC8**), *S*)-3-((hydroxyimino)methyl)-1-(2-((1-(octylamino)-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)pyridin-1-iumbromide, **3-PyPheC8**), and (*S*)-4-((hydroxy-imino)methyl)-1-(2-((1-(octylamino)-1-oxo-3-phenylpropan-2yl)amino)-2-oxoethyl) pyridin-1-ium bromide, **4-PyPheC8**) moiety. Their biodegradability examined in the closed bottle test shown the dependence on the amino acid structure and follows the tendency Phe> Ala> amide. Phenelalanine-based oximes demonstrate >30% of degradation in the CBT after 42 days and can be considered as inherently degradable. The acid ionization constant (pK_a) of studied oximes determined by means of UV-vis spectroscopy at 27 ˚ C were found to be in the range from 8.00 to 9.00. The p$K_{a,app}$ values of oximes in the presence of cationic gemini surfactants, 12-4-12- and 16-10-16, change insignificantly whereas they shifted upwards in the presence of anionic surfactant SDS. The nucleophilic cleavage of organophosphorus triester PNPDPP under optimal concentration conditions of **4-PyC8** come about with half-life times 40 s under mild condition (pH 9.00). These results provide new information on control the green microorganized nucleophilic systems for chemical decontamination.

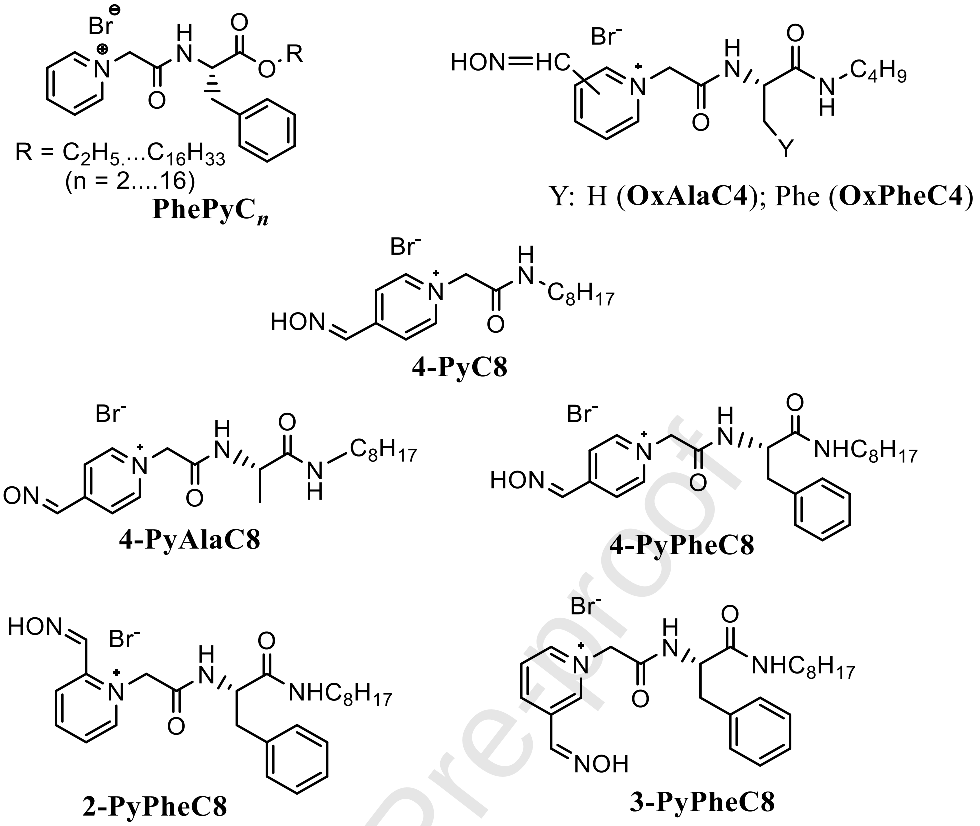
Keywords
Ionic liquids; oximes; biodegradability; closed bottle test ; acid dissociation constant ; chemical decontamination.

1. Introduction

Ionic liquids (ILs) are increasingly seen nowadays as an integral part of green chemistry applications [1-3] with a particular attention to their biocompatibility and biodegradability [4-7]. An attractive feature of ILs is the ability to refine the structure, to tailor the properties for a desired application. The ILs with long chains are capable to form aggregates in aqueous solutions similar to that of conventional surfactants and are called the surface-active ionic liquids (SAILs) [8, 9]. This overlapping between surfactant and IL chemistry causes the increased interest to the synthesis, self-organization, and applications of SAILs, including developing micellar catalytic systems [10, 11]. Progress in the development of biodegradable ionic liquids ILs allowed finding sustainable fragments to assist the synthesis of sustainable molecules by means of “benign by design” approach [12, 13]. The novel SAILs are expected to combine advanced colloid properties with lowered risk for the environment [14]. We have reported recently a versatile approach towards the synthesis of biodegradable amino acid derived ILs [12, 13] to open the opportunities for developing SAILs with optimized environmental toxicity [15] and tunable properties [16] in their self-assembly, antimicrobial activity, and biodegradability. Among the L-phenylalanine (Phe) derived SAILs reported in our recent report [16], the medium chain length (namely, *n*-hexyl and *n*-octyl esters) derivatives bearing pyridinium headgroup were pointed out to be the prospective green alternatives for conventional surfactants and to be considered as the base for miscellaneous applications.

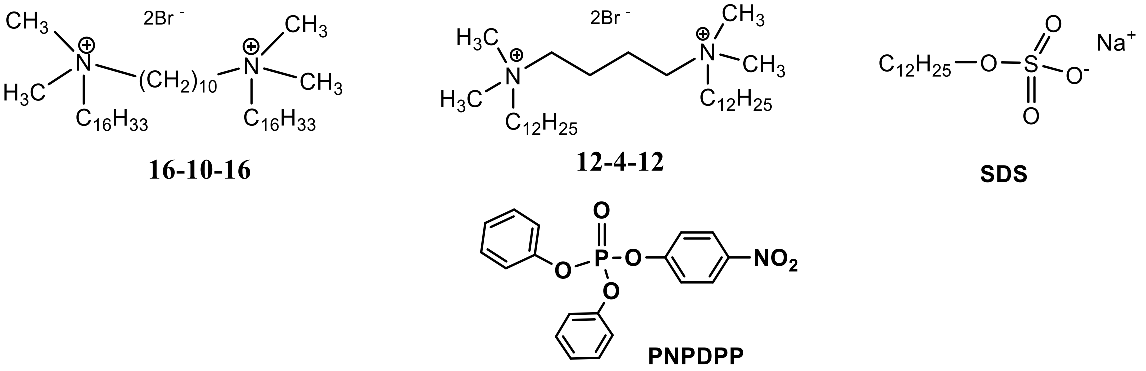
A problem of both theoretical and practical importance is the fast and irreversible detoxification of organophosphorus compounds (OP), either used as pesticides or chemical warfare agents (CWA) [17-21]. The comprehensive approach of solving problems related to the crisis management, e.g. remedial measures to mitigate manmade disasters or a terrorist attack towards civilians [22, 23] is also far from complying with the principles of green chemistry. During an incident involving exposure of civilians, it's usually exists a delay between initial exposure of poisonous agents and on-scene arrival of the effective countermeasures and trained personnel to apply best military practices [17]. Formulations, which are environmentally friendly and easy-to-use by both first responders or volunteers are on demand, and they are far from being fully fitted to the green chemistry criteria. The significance of the international efforts towards environmentally benign methods of chemical decontamination was sharply highlighted by the OPCW’s Initiative on Green and Sustainable Chemistry [24] aimed at enhancing implementation of the Chemical Weapons Convention.

The non-functionalized SAILs aggregates have been published to solubilize OP pesticides [25] or act as micellar hydrolytic system bringing together OP pesticide and a weak nucleophile in the micellar pseudophase [26]. Oximes are among the most effective nucleophiles providing high rate of the detoxification of OPs under mild pH [27-29]. One of the promising ways to advance micellar catalytic system is attaching specific functional moiety to the surfactant headgroup. It allows one to produce high “local” concentration of the reactive species in the region close to the micellar interface [30]. The commonly used antidotes [31, 32] and functionalized surfactants [33] for effective cleavage and degradation of toxic organophosphorus compounds (OP) are zwitterionic salts (in their reactive form oxime group is deprotonated) containing quaternary ammonium (pyridinium, in essence) group. The results on studies of oxime supernucleophilic systems in the reactions toward toxic organophosphorus esters have been rationalized in a terms of micellar kinetic in relation to the oxime structure and basicity [31, 34-39]. The CMC values for the Phe-derived SAILs reported in [16], see Scheme 1, are significantly (up to 10 times) lower than those for conventional surfactants with the same length of the side chain. This phenomenon was supposed to be related with the role the aromatic ring of Phe moiety plays in the aggregation. The pyridinium headgroup non-functionalized Phe-derived ester IL with *n*-butyl chain (R= C_4H_9) has considerably high, as for practical use, CMC value of ≥60 mM, but *n*-octyl derivative (R= C_8H_{17}) was reported to demonstrate CMC ca. 2 mM that is comparable with much less (bio)degradable conventional cationic surfactants with tetradecyl or hexadecyl chains. Combined with data on toxicity and biodegradability [15, 16], it makes octyl derivatives among the most suitable SAILs for practical applications. The short-chain Phe-derived oxime (*n*-butyl esters and amides, see Scheme 1) have been recently reported as the potential antidotes-reactivators of human acetyl cholinesterase inhibited by OP insecticide paraoxon and nerve agents sarin and VX [40]. Our approach presented in this work includes extension of the side chain of the hydroximinopyridinium IL-based short-chain salts [40] in order to obtain amphiphilic oximes /functional surfactants [41], which may lead to the environmentally benign micellar systems for chemical decontamination [31]. Since oxime possess alpha effect properties in its deprotonated form, the acid dissociation constant (pK_a) [29] is an important physicochemical parameter to analyze the “effective pH” allowing oximate ion (zwitterionic species of the structures represented on the Scheme 1) attack the unsaturated center of a substrate [42, 43]. The apparent pK_a of oxime values may vary in the presence of an added surfactant of different structure in the mixed micellar systems [38, 39].



Scheme 1. Phe-derived non-functionalized SAILs [15] (top left), their short chain oxime-functionalized antidotes [34] (top right), and oxime-functionalized IL-derived surfactants with *n*-octyl chain reported in this work.

Analysis of acid-base equilibria of the environmentally benign amphiphilic oximes and observed effects towards OP, either real agents or their low toxic simulants, may give a clue to the designing biodegradable constituents for chemical decontamination systems.



Scheme 2. Structure of surfactants and OP substrate used in the present work.

We report here the synthesis and characterization of a series of novel IL-derived amphiphilic oximes **4-PyC8**, **4-PyAlaC8**, **2-PyPheC8**, **3-PyPheC8**, and **4-PyPheC8** (Scheme 1) followed by the studies of their biodegradability under aerobic aquatic condition using Closed Bottle Test (OECD 301D). We present determination of pK_a values of oximes studied in the bulk and in the presence of gemini (16-4-16 and 12-10-12) and anionic (SDS) surfactants (see Scheme 2), along with kinetics of the oximolysis of model OP, 4-nitrophenyl diphenyl phosphate (PNPDPP) in the presence of one of the above surfactants at “mild” pH values of 8.35 and 9.00.

2. Experimental Section

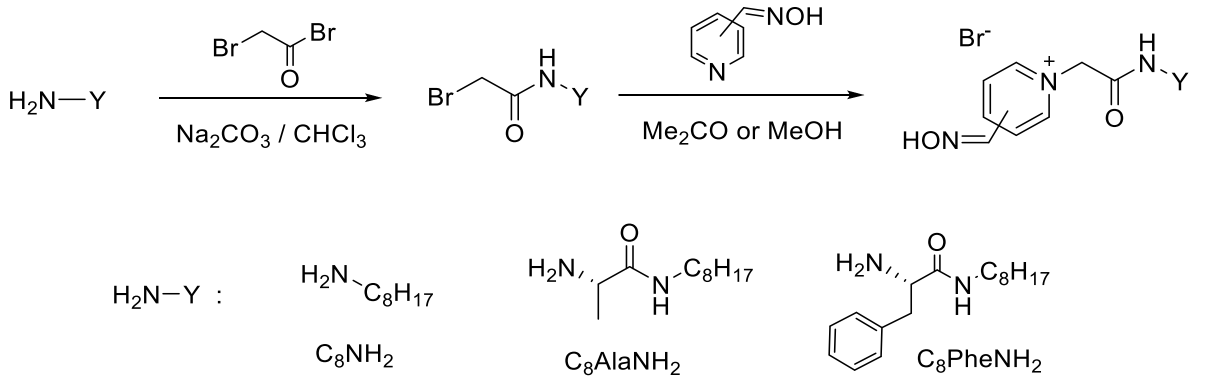
2.1 Materials

All commercial chemicals and solvents were purchased from Sigma Aldrich, Alfa Aesar, or TCI Europe and used without further purification. Silica gel 60 F254 plates were used for TLC. Gemini surfactants were synthesized in the laboratory of Dr. P. Quagliotto, Department of Chemistry, University of Torino, Italy. PNPDPP was prepared at Defence Research Development Establishment, Gwalior (India), sodium dodecylsulphate (SDS), potassium dihydrogen phosphate and dipotassium - hydrogen phosphate were purchased from Sigma - Aldrich and used without further purification. All the reagents used were of analytical grade. Double distilled or demineralized water was used throughout the experiments.

2.1.1. Characterization of products. Melting points were determined with Stuart SMP40 apparatus with parameters for the melting point analysis set at 2°C per minute ramp; values are expressed in °C. The HRMS identification of compounds was performed on Agilent 6540 UHD Accurate-Mass Q-TOF LC/MS G6540A Mass Spectrometer. Bruker Avance III 400 MHz spectrometer operating at 400 MHz for ^{1}H-NMR and 101 MHz for ^{13}C-NMR. Samples were recorded in deuterated chloroform ($CDCl_3$) or dimethyl sulfoxide (DMSO-d_6) where appropriate. All chemical shifts δ are reported in parts per million (ppm) are relative to the internal standard TMS and coupling constants (J) are measured in Hertz (Hz).

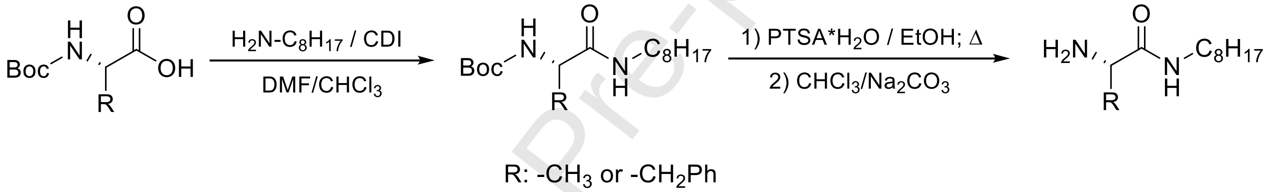
2.1.2. Synthesis of the IL-derived amphiphilic oximes

We report synthesis of the series of novel SAILs-derived oximes obtained from corresponding amines similar to a general Scheme 3 similarly to the method published for amide ILs [44, 45] and a series of L-phenylalanine (Phe) ILs we have published previously [13, 16]



Scheme 3. General method of synthesis of oximes studied in this work.

Precursors C_8AlaNH$_2$ and C_8PheNH$_2$were synthesized from corresponding commercially available Boc-protected amino acids (see Scheme 4).



Scheme 4. Synthesis of key precursors for studied oximes.

Boc-protected octylamides. The corresponding N-(Boc)-L-amino acid (0.05 mol; Boc-N-Phe or Boc-N-Ala) was dissolved in dry DMF (25 mL) under argon atmosphere and the reaction mixture was cooled to 0ºC. Then to stirred solution was added portionwise carbonyldiimidazole (8.11 g; 0.05 mol). The reaction mixture was stirred 15 min more after stopped of gas formation. After that, solution of 1-octylamine (8.26 mL; 0.05 mol) in alcohol-free amilene-stabilized chloroform (25 mL) was added dropwise to reaction mixture. The reaction mixture was stirred 24 hours at room temperature under argon atmosphere. After that, solvents from reaction mixture was evaporated *in vacuo*, residue dissolved in chloroform (100 mL) and washed with 0.1 N HCl (2 x 50 mL), 0.1 N Na_2CO_3 (2 x 50 mL) and water (2 x 50 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford the title compounds. The yields were 95–97 %.

Boc-deprotection of C_8AlaNH$_2$ and C_8PheNH$_2$). To a solution of corresponding N-(Boc)-L-amino acid octyl amide (0.05 mol) in ethanol (150 mL) was added PTSA·H_2O (12.36 g; 0.065 mol) and refluxed with stirring for 12 hours. Then solvent was removed *in vacuo*. Residue was dissolved in chloroform (150 mL) and washed with solution of Na_2CO_3 (0.1 mol; 10.6 g) in water (150 mL), and then with water (2 x 100 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford the title compounds (yield 96–98 %).

Synthesis of N-bromoacetyl derivatives.To a stirred solution of the corresponding substituted amine (0.05 mol) in alcohol-free chloroform (50 mL) was added solid Na_2CO_3 (7.95 g, 0.075 mol). To this mixture was added dropwise bromoacetyl bromide (5.65 mL, 0.065 mol) and stirred for 12 hours. Then 50 mL of water added carefully to reaction mixture and then transferred to a separating funnel. The organic layer was separated, washed with 0.1 N Na_2CO_3 (2 x 50 mL) and water (3 x 50 mL). The organic phase was dried over sodium sulphate, filtered, and volatiles were removed *in vacuo* to afford the title compounds. The yields were 94–98 %.

Synthesis of pyridinium aldoximes. The stirring solution of corresponding N-bromoacetyl derivative (0.01 mol) and corresponding pyridinealdoxime (1.22 g; 0.01 mol) in 25 mL of acetone (for 2- and 3-pyridine aldoxime) or 25 ml of methanol (for 4-pyridinealdoxime) was refluxed for 12 hours. After cooling to room temperature the solid product was filtered, washed with cold acetone(3 x 10 mL), then with diethyl ether (2 x 20 mL), and dried *in vacuo*. The titled compounds was isolated with yields 38 – 70 %. ^{1}H and ^{13}C NMR spectra, HRMS and mp of the obtained compounds are collected in the **Appendix A**.

2.2 Methods

2.2.1. Aerobic biodegradation test.

Biodegradation was studied using the Closed Bottle Test (CBT) method OECD 301D described in the previous papers [12, 13]. Effluent from wastewater treatment plant was collected from a municipal wastewater treatment plant in Tallinn, Estonia (Paljassaare wastewater treatment plant, 59°27'55.5"N 24°42'08.8"E). WWTP effluent was filtered through a Whatman cellulose filter paper (90 mm diameter, Grade 1, pore size 11µm) before being used as inoculum. Aerobic biodegradation testing was done using modified CBT (OECD 301D). CBT setup with modification where biological oxygen consumption is measured with an optode oxygen sensor system using PTFE-lined PSt3 oxygen sensor spots (Fibox 3 PreSens, Regensburg, Germany) allows measuring BOD without opening the flasks and thereby reducing the number of parallels needed for each compound and increasing test throughput. It has also shown to improve reproducibility compared to the original OECD 301D guideline [46]. Each CBT run consisted of four different series, each have been repeated in duplicates. First was „reference series“ in which readily biodegradable sodium acetate in known concentration (6.41 mg L^{-1}) was added to a flask of mineral medium inoculated with effluent from wastewater treatment plant. In „test series“ test compound, as a source of carbon was added to the inoculated mineral medium. The test compound was added in concentration corresponding to theoretical oxygen demand (ThOD) of approximately 5 mg/L. ThOD was calculated assuming nitrification would take place as each of the 25 studied compounds included nitrogen atom(s) in their structure. „Toxicity series“ containing both sodium acetate and test compound in their respective concentrations were used to evaluate test compounds’ toxicity against inoculum – if biodegradation values in these bottles were significantly lower compared to reference series it was concluded that test compound could be inhibiting or even toxic to microbes in WWTP effluent. Each run was extended from 28 days (suggested by OECD 301D protocol) to 42 days.

Results from each run were accepted if following criteria were met: i) difference of extremes of replicate values at the plateau is less than 20%, ii) oxygen concentration in test series bottles must not fall below 0.5 mg/L at any time, iii) sodium acetate in reference series must be degraded ≥ 60% by day 14. Blank bottles oxygen consumption was also monitored to avoid possibility of system turning from aerobic to anaerobic

2.2.2. pH measurements

The pH of the buffer solutions was determined using a pH meter Eutech pH 700, equipped with an Inlab@ Expert Pro glass electrode with an accuracy of ±0.01 units. The pH meter was calibrated using the two-point calibration method with commercially available standard buffer solutions at pH 4.00 and 9.00.

2.2.3. UV-Visible spectroscopy

The spectrophotometric measurements were recorded by Cary 60 UV–Vis spectrophotometer (Agilent Technologies) in the range of 200 – 400 nm. All the spectra were recorded at 27 °C. The solutions of different pH (6.20-10.50) were used in spectrometric analysis. The quartz cells were attached to Peltier element for maintaining the constant temperature (27 ± 0.5 °C). The stock solution of the oxime-functionalized salt **4-PyC8** was prepared solution in water, and the stock solutions of other oximes **4-PyAlaC8, 2-PyPheC8**, **4-PyPheC8**, and **3-PyPheC8** were prepared in 25% (v/v) ethanol-water, as they were sparingly soluble in water. An aliquot of 3 mL from stock solution of 0.5mM of oxime in double distilled water was diluted with 25 mL phosphate buffer solution of pH 6.2 and the spectrum was recorded using buffer solution as a blank. The pH was calibrated to the desired value by using sodium hydroxide (NaOH) solution. After balancing each pH, the absorption spectra were recorded at selected wavelengths 200 to 400 nm (Fig. 1). Similarly, the effect of surfactants (gemini and anionic) with functionalized oximes based ionic liquids were done. The concentration of surfactants was 10 mM.

2.2.4. Determination of acid dissociation constant (pK_a)

The pK_a values of all oximes studied in this work have been determined by spectrophotometric method described by Albert and Sergeant [47]. All the spectrophotometric measurements were made at 27 °C and the spectra were recorded within the range of 200-400 nm. The absorbance spectra of all the compounds where noted in aqueous solution **4-PyC8** and in 25% (v/v) ethanol-water **4-PyAlaC8**, **2-PyPheC8**, **4-PyPheC8**, **3-PyPheC8** of different pH, see Fig 1. The shorter wavelength absorption maximum, appearing at lower pH values, reflects the absorption of the non-ionized oxime group(s) in all investigated compounds, whereas the longer wavelength maximum, observed at higher pH values, is due to the absorption of the reactivator with an ionized oxime group(s). The pH-dependent absorption spectra show the presence of isosbestic point. The pK_a values have been evaluated from the absorbance *vs*. pH data by the general method of Albert and Sergeant using eq. 4.

The ionization behavior of oxime may be represented as,

$$\mathrm{HA} \rightleftharpoons \mathrm{H}^{+} + \mathrm{A}^{-} \tag{1}$$

Then the apparent acidity constant $K_a$of the acid HA is defined as the equilibrium constant

$$K_\mathrm{a} = \frac{[\mathrm{H}^{+}]\,[\mathrm{A}^{-}]}{[\mathrm{HA}]} \tag{2}$$

By taking the logarithms and reconstructing the equation. (2) we get the Henderson- Hasselbalch equation

$$\mathrm{pH} = \mathrm{p}K_\mathrm{a} + \log\frac{[\mathrm{A}\text{-}]}{[\mathrm{HA}]} \tag{3}$$

This equation can be written as shown in equation (4)

$$\mathrm{p}K_\mathrm{a} = \mathrm{pH}_\mathrm{exp} - \log\frac{\mathrm{Abs}_\varphi - \mathrm{Abs}_\mathrm{HOx}}{\mathrm{Abs}_\mathrm{Ox} - \mathrm{Abs}_\varphi} \tag{4}$$

where, $\mathrm{Abs}_\mathrm{HOx}$ is the absorbance of unionized form of an oxime, Abs_Ψ is the absorbance of partially ionized form of oxime, and Abs_Ox is the absorbance of completely deprotonated form of oxime at particular pH.

2.2.5. Reaction kinetics

The pseudo-first order rate constants for the hydrolysis of PNPDPP phosphate esters in the presence of different composition of concentration of the oxime **4-PyC8** were determined at 8.35 and 9.00 pH at

27°C. The reaction were monitoring as the appearing of the leaving *p*-nitrophenoxide anion at wavelength 400 nm shown in Fig. 1 recorded by Cary 60 UV–Vis spectrophotometer (Agilent Technologies) with a temperature controller (Peltier element). Phosphate buffer (0.1 M) was employed to control the pH for all the reaction process. All the pH measurements were obtained using a pH meter Eutech pH 700, equipped with an Inlab@ Expert Pro glass electrode with an accuracy of ±0.01 units. All kinetic reactions were conducted under pseudo-first order conditions, i.e. with large excess of oximate anions over the PNPDPP.

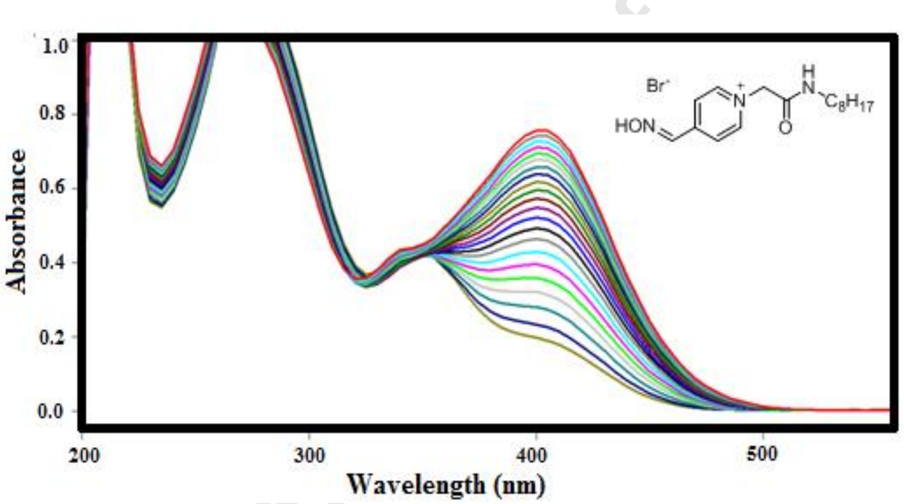


Fig. 1. UV-vis spectra collected at different reaction times showing the increase in absorbance of *p*-nitrophenoxide anion for the cleavage of PNPDPP with **4-PyC8**.
[PNPDPP] = 0.5 mM; [**4-PyC8**] = 1.0 mM; pH 9.00; 27 °C.

Each experiment was repeated until observed rate constants were reproducible within an accuracy of ±5% or better. For all the kinetic reaction run, the plots of absorbance verses rate results fits very well for the first–order rate equation (5).

$$\ln(A_\infty - A_t) = \ln(A_\infty - A_o) - kt \quad (5)$$

The progressive reaction of pseudo-first–order rate constants (k_{obs}) were determined from the plots of absorbance verses time with A_0, A_t, and A_∞ being the absorbance significance at zero, time and infinite time, respectively. The substrate (PNPDPP) concentration was being kept constant for all the kinetic runs (0.05 mM). The reaction were performed at various concentration of functionalized oxime-based **4-PyC8** to explore the effect of an amphipnilic oxime on the cleaving potency of PNPDPP.

3. Results and Discussion

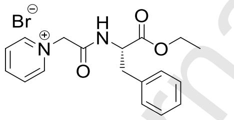
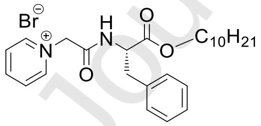
3.1. Biodegradability of IL-derived oximes

Studies into the ultimate biodegradability of studied amphiphilic oximes have been set a requirement for implementation of the EU regulation on detergents [48]. Ultimate biodegradation, or mineralisation, is achieved when the test compound is totally utilized by microorganisms (inoculum) resulting in the production of primarily carbon dioxide, water, mineral and salts. In the stringent tests, such as CBT, it is used to operate the term "readily biodegradable" for those chemicals which have passed CBT showing 60% of biodegradability or more. It is assumed that such compounds will rapidly and completely biodegrade in aquatic environments under aerobic conditions. Compounds for which there is unequivocal evidence of biodegradation in the extent from 20% to 60% are called inherently biodegradable. An extension of the time of the experiment (e.g. from the standard 28 days to 33 or 42 days) may provide an additional insight into the inherent biodegradability of the sample. The "traffic light" classification [49] is used to facilitate recognition of the certain biodegradability, to place the green light for readily biodegradable chemicals, amber light for inherently biodegradable, and red light – for those that have not reached 20% threshold of the biodegradability during the test.

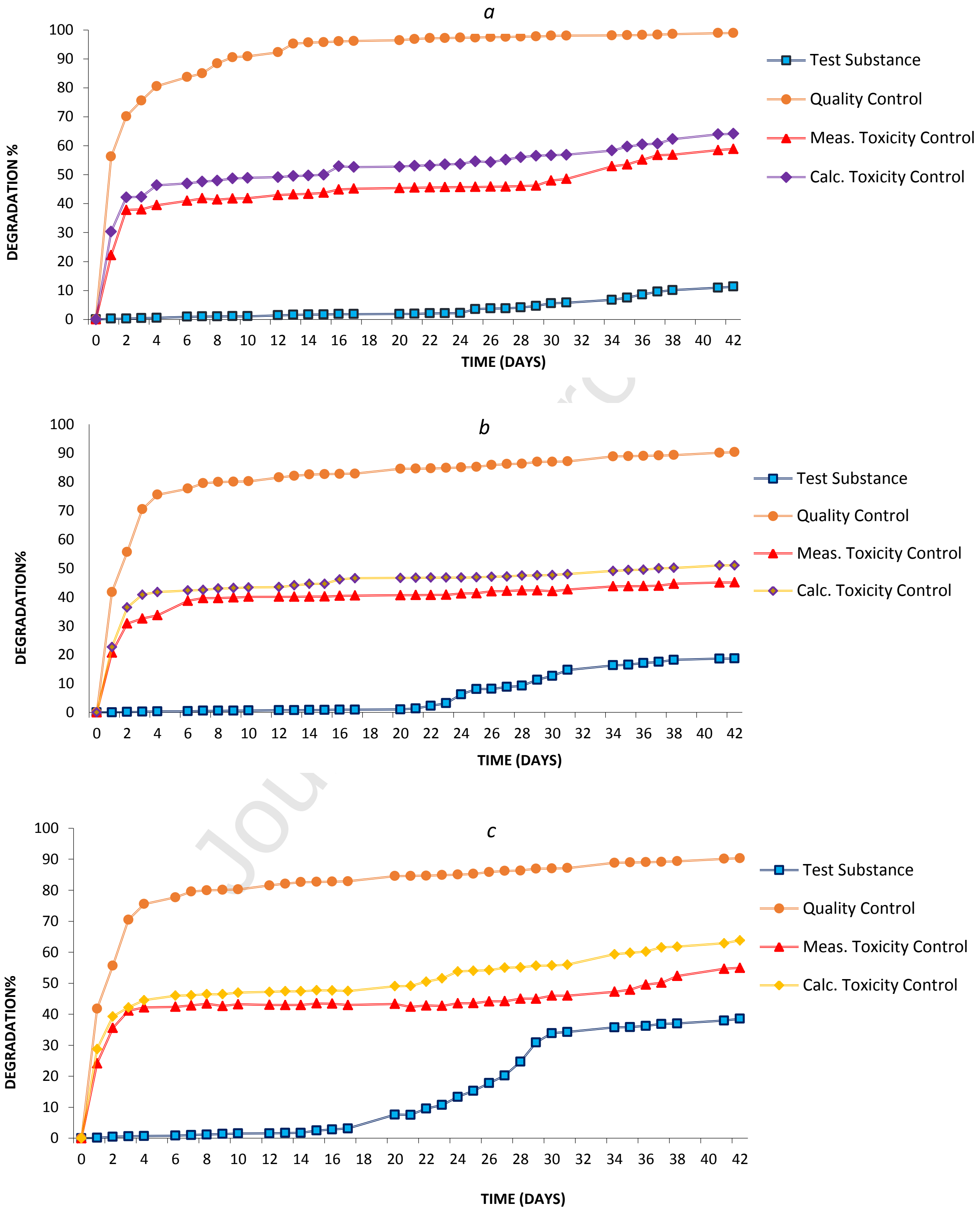
The studied oximes have different solubilities in water so only in the case of **4-PyC8** water was used to prepare its stock solution. For the oximes **4-PyAlaC8**, **2-PyPheC8**, **3-PyPheC8**, and **4-PyPheC8** the DMSO was added along with MilliQ water to overcome this solubility issue and prepare their stock solutions. To negate the effect of inoculum, blank bottles containing only inoculum and mineral medium were added to the CBT run and the values of these bottles were subtracted from other bottles of IL-derived oximes ("blank DMSO"). Another set of DMSO constituting blank was also added to negate the effect of inoculum and DMSO. The data on CBT within 28 days and 42 days are collected in the Table 1. It's worth noting that none of the samples passed CBT within 28 days whereas extension to 42 days demonstrate tendency of the studied salts to biodegrade, see Table 1, Fig. 2, and Fig. S1-S2. The amide salt **4-PyC8** demonstrate low biodegradability (11%) even after 42 days, even since the biodegradation slightly accelerates (ascending curve to develop) after the induction period about 20 days of the no plateau reached yet upon the 42 days, see Fig. 2*a*. Alanine derivative **4-PyAlaC8** shows better results (19% after 42 days) but not overcoming 20% threshold, Fig. 2*b*. All three phenylalanine derivatives demonstrate comparable tendency to biodegradability: 20% (**3-**

PyPheC8), 24% (**2-PyAlaC8**), 25% **(4-PyAlaC8**) after 28 days, and 34% **(3-PyPheC8),** 37% **(2-PyAlaC8),** and 39 % **(4-PyPheC8)** after 42 days, Fig. 2*c*, Figs. S1-S2. The biodegradability for all oximes are inferior to that of the parent phenylalanine SAIL, see Table 1. Thus, short-chain ethyl Phe IL is a readily biodegradable (mineralisible) compound within standard 28-days CBT [12, 13], and the decanoyl (C10) derivative SAIL can be characterized as inherently biodegradable based on 28-day run [16]. The data presented in Table 1 confirms that the Phe ILs-derived oximes can be considered as inherently biodegradable amphiphiles.

Table 1. CBT results on biodegradability of studied oximes and their non-functionalized Phe-derived IL precursors; color coded according to the traffic light classification [49]

Structures	**D% 28 days**	**D% 42 days**
4-PyC8	**4**	**11**
4-PyAlaC8	**9**	**19**
2-PyPheC8	**24**	**37**
3-PyPheC8	**20**	**34**
4-PyPheC8	**25**	**39**
 **PhePyC2**	**63 [13]**	**-**
 **PhePyC10**	**36 [16]**	**-**

There are several possible resons causing lower biodegradability for the IL-derived oximes, compared to parent ILs. The PhePyCn salts reported in our recent paper [16] have been prepared based on the Phe esters (from C2 to C16), and are not tolerant to the nucleophilic attack of OH^- under alkaline conditions or to the esterolysis by oximate ion. To expand the window of pH for potential application (chemical decontamination, in essence), the C8 oximes have been prepared as amides, toltertant to hydrolysis in the wide interval of pH. Enzymatic cleavage of the amide bond of the shorter chain salts (C4) by the inoculum microorganisms occurs slower than esterolysis [50].


a
b
c
DEGRADATION %
DEGRADATION%
TIME (DAYS)
0
10
20
30
40
50
60
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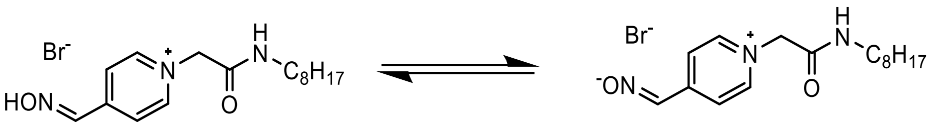
Test Substance
Quality Control
Meas. Toxicity Control
Calc. Toxicity Control

Fig. 2. Biodegradability data for 42 days CBT experiment; *a* - **4-PyC8;** *b* - **4-PyAlaC8;** *c* - **4-PyPheC8**

An additional factor one should take into account is an order of cleaving two amide bonds present in the IL-derived oxime stucture. It was pointed out [13] that it is amide bond from the N-side of Phe to be cleaved first to provide readily biodegradation of the **PhePyC2** salt. Cleavage of the C-side bond resulted in accumulation of the corresponding pyridinium linked phenylalanine carboxylic acid that is more persistent than pair of the transformation product Phe-ester (Phe-amide) + N-carboxymethylpyridinium salt. Another reason of the retardation of biodegradation as compared to the parent ILs could be introducing oxime moiety into the pyridinium ring that makes the biotransformation process more complex, as compared to pyridinium itself. The abilities of most fungi and bacteria to metabolize Z-oximes to use them as a source of reduced nitrogen is described eslewhere [51], the most usual mechanism to be conversion into the corresponding nitrile, amide, and carboxylic acid with a concomitant release of ammonia. Therefore, this process is expected to occur in the presence of oximinomethyl pyridinium salts irrespectively of the side chain structure. Indeed, the position of the oximino moiety does not affect the CBT results. At the same time, the biodegradability is dependent on the amino acid structure and follows the tendency Phe> Ala> amide. This tendency supports that the introducing amino acid fragment into the surfactant structures increases its biodegradability, compared to the amide salts. We suggest that better biodegradability of the Phe-containing salts as compared to Ala analogs may be related to facilitated enzymatic aminolysis of the Phe salts as the first transformation stage. Therefore, the Phe-containing oximes are the most promising functional compounds in the series. Due to their inherent biodegradability, they can be among prospective candidates for environmental application, in particular, to use as a basis for chemical decontamination formulations. Even if they did not fulfil the criterion of ultimate biodegradation within the stipulated period, these amphiphilic oximes can be considered, according to current detergent regulation [48] for special applications, i.e. those the chemical decontamination can be referred to.

3.2. Acid dissociation constant (pK_a)

The acid base equlibrium of oxime can be represented as below (Scheme 5).



Scheme 5. Schematic representation of the acid-base equilibrium of the amphiphilic oxime **4-PyC8**.

A number of approaches have been used to determine the pK_a value including potentiometry, conductometry, spectrophotometry, solubility, and liquid–liquid partitioning. Out of all the techniques UV–Vis absorption spectrophotometry is used to be more reproducible and required lesser amount of analyte. This technique requires very low analyte concentrations and can measure absorbance in aqueous solution even for products with low solubility in water [52-57]. There are number of the studies on oximes with reported pK_a values determined by means of spectrophotometry in water [28, 58] as well as in aqueous mixture with organic solvent [29] (e.g. 50% (v/v) water-acetonitrile [58]). Mixture of water with water-miscible organic solvent are used to apply to determine the pK_a values for compounds imperfectly soluble in water [59-62]. We considered the average values of ten measurements as the pK_a of the compound with respect to oxime group, following the recommendations of the paper [63].

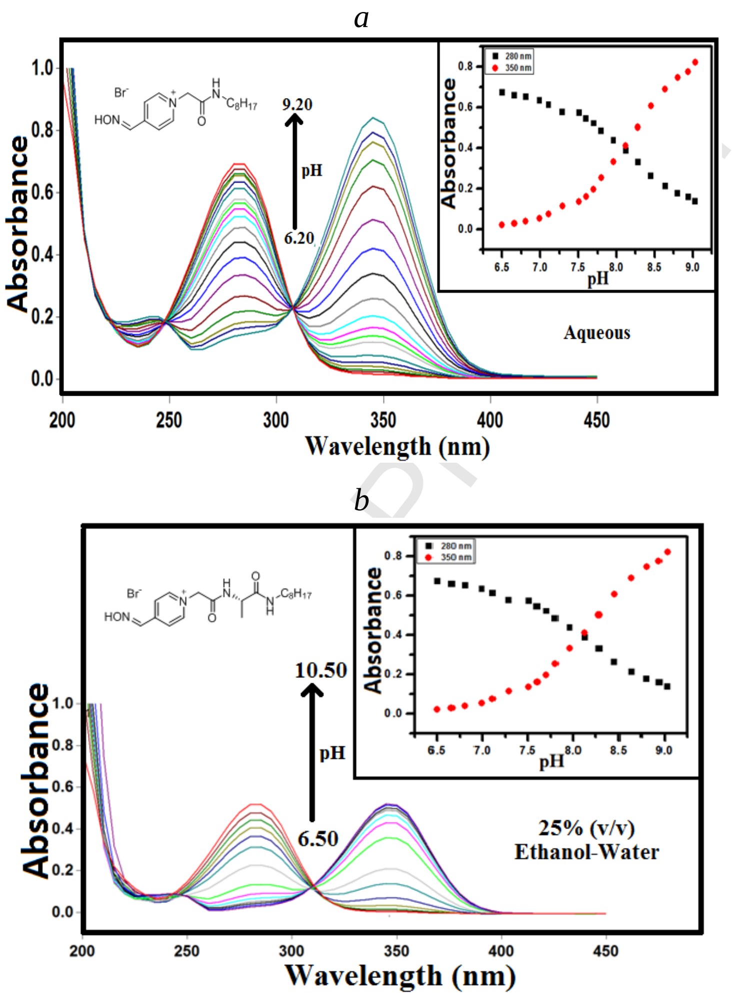
The absorption spectra of different oximes at various pH values 6.20 - 10.50 are shown in Fig. 3. The change in the absorption spectra with the change in the pH indicates that the dissociation of the oxime group into the oximate occurs in the studied pH range. The absorption spectra of all studied salts show mainly two pH dependent absorption maxima: (i) the shorter wavelength absorption maximum, appearing at lower pH values in the range from 280 to 300 nm, reflects the absorption of the non- ionized oxime group in all the analyzed compounds, (ii) the longer wavelength maximum, observed at higher pH values in the range from 345 to 350 nm, is due to the absorption of the ionized oxime group [64]. Both maxima are in accordance with the change of $\pi \rightarrow \pi^*$transitions within the aromatic ring of pyridinium ring. Upon increasing the pH, the absorbance of the shorter band decreases, while that of the longer band increases. A typical effect of pH on the absorption spectra of all functionalized oxime based ionic liquids were reflected by the dissociation of either oxime groups exhibits a well organized by overlapping ionization equilibria i.e., isosbestic point at 310 nm denoting the existence of an equilibrium essentially an acid base between the NO^- , which has an absorption maximum at 345 to 350 nm and the other form NOH, which has an absorption maximum at 280 to 300 nm [64]. It was observed that the resulting pK_a values revealed that pH of the oximes were between the pH range of 7.89-8.48 which had the oxime group at ortho and para position whereas when the oxime was present at meta position its pH was found to be have pK_a values 9.00. The pK_a values are collected in Table 2.

The absorbances of **4-PyC8** at 280 and 350 nm, for **4-PyAlaC8** at 280 and 350 nm, for **2-PyPheC8** at 300 and 350 nm, for **4-PyPheC8** at 285 and 345 nm and for **3-PyPheC8** at 245 and 290 nm were plotted against pH values of the buffer solution shows the solid curves represent the non linear regression square fit curves (inset of Fig. 2) is obtained. It was seen that the pK_a of **3-PyPheC8** (9.05) was moderately higher as compared to the pK_a of **4-PyC8**, **4-PyAlaC8**, **2-PyPheC8**, and **4-PyPheC8** (8.08-8.48) were found to be in lower range. These differences in the pK_a values can be explained with the help of resonating concepts in which the meta position of oxime group of **3-PyPheC8** having comparatively lesser resonating structure than that of **4-PyC8**, **4-PyAlaC8** and **4-PyPheC8** in which oxime having oximino group at para position and compound **2-PyPheC8** having oximino group at *ortho* position respectively. As they proceed through a resonating structure where the positive charge of pyridinium ring have established oneself on the carbon atom at second and forth (*ortho* and *para* position) isomers. These circumstances allow oxime to demonstrate more remarkable electron withdrawing effect as compared to **3-PyPheC8**, i.e, third isomer (meta position) which lead to the lower pK_a values of second and forth (*ortho* and *para* position) isomers [63]. Apparently, the pK_a value was ruled by the position of oximino function in pyridinium ring and the position of linker had a little effect in corresponding pK_a value. In structure of functionalized oxime based ionic liquid, presence of oxime along with their position (*ortho* and *para*) play an important role on the reactivation and detoxification of OP compounds [33].

3.2 Effects of added surfactants on the p$K_{a,app}$ of oxime

The micellar systems can be regarded to be a system consisting of an aqueous phase and a micellar pseudophase [65, 66]. Micelles can influence the pK_a values of protogenic groups due to the combination of electrostatic and minute environmental effects of the micellar system [67-70]. The effect of micellar systems on acid-base equilibria has been suggested to arise from an intrinsic factor (due to the energy difference between the aqueous and the nonpolar media) and a potential effect that is due to the electrically charged micellar surface [68].

The incorporation of the studied oximes into the mixed surfactant aggregate can affect their the acid-base equilibrium. The appeared effects will depend on hydrophilic-lipophilic balance of oxime amphiphile and nature of micellar surface [67]. For analysis of this influence we have chosen two gemini surfactants with different properties of the aggregate surface (12-4-12, 16-10-16) and one anionic surfactant (Scheme 2) and have studied an ionization process in pH range 6.20 - 10.50. The absorption spectra are shown in Fig. 4. The pK_a for each wavelength was calculated using Eq. 4. The pK_a values of studied salts, which were determined without any added surfactant, are used as a reference in presented analysis, see Table 2.



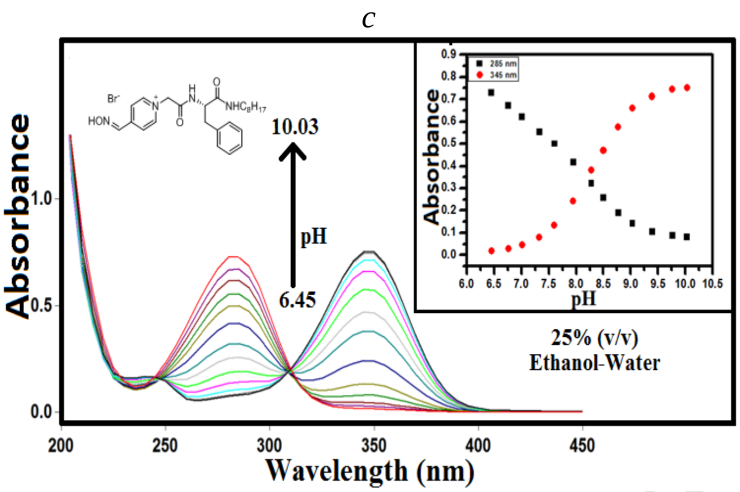


Fig. 3. Representative absorption spectra of oximes (*a* – **4-PyC8**; *b* – **4-PyAlaC8**; *c* - **4-PyPheC8**; at different pH values; water, 27 °C. Inset: plots against pH and absorbance for oximes in aqueous solution of $[Ox]_0$ = 50 mM; pH = 6.20...10.50.

The data indicate that the interchange of the neutral form of functionalized oxime based ionic liquids (HA) is stronger than that of the anionic species (deprotonated oximes A^-) [71]. The effect of SDS on the observed dissociation constant of oxime based ionic liquids, having higher pK_a. It is of interest to explain the increase in the pK_a values in the micellar phase, because SDS as an anionic surfactant and form the anionic micelles so as to concentrate the protons in the aggregate's interface and slightly suppressed the protonation of the aromatic oxime group [72-74].

The presence of cationic surfactants in mixed micellar system with oxime-functionalized surfactants was reported previously elsewhere [37, 39] to cause decreasing of apparent pK_a value (p$K_{a,app}$) of the oxime moiety. In this study, we did not report a significant effect of the surfactant on the deprotonation constant, they remain within the standard experimental errors, see Table 2. We also report here that the role of the gemini head group structure on the pK_a of oximes is negligible, in spite of the fact that 12-4-12 with relatively rigid spacer tend to form different aggregates as compared to 16-10-16, gemini surfactant with a long flexible spacer. We may suggests that levelling this difference off is a result of interaction of amide bond with micellar surface repulsing oxime moieties outside the micellar surface. The moderate hydrophobic properties of *n*-octyl chain and introduction of the amino acid fragments (in essence, hydrophobic phenyl ring of Phe promoting micellization of the Phe SAILs [16], see Scheme 1), the factors promoting micelle formation, seems not to be factors sufficient to outweigh this interaction and move oxime moiety closer to the micellar surface. SDS increased basicity of the hydroximino groups could be explained in terms of electrostatic interactions at the negatively charged SDS aggregate interface (anion repulsion and cation attraction). This surfactant affected the oxime group of all examined functionalized oxime based ionic liquids in the same manner; that is, an increase of basicity due to its negatively charged interface acted to stabilize the protonated hydroximino group. Decreasing apparent oxime basicity in the presence of anionic SDS suggested hydrophobic interactions under the experimental analysis and lipophilic hydrocarbon chain that takes oxime group apart [74]. In other words, these two effects are against each other and showed higher variation in the pK_a values. The positively charged pyridinium headgroup undergo repulsion in the interaction to the cationic gemini headgroups so hydrophobic interaction remain the only driving force to form the mixed aggregates in such a system. This may not cause sufficient shift of the p$K_{a,app}$ value of the oxime group.

Table 2. Acid dissociation constants of studied oximes in the absence and in the presence of surfactants; 27 °C, $[D]_0$= 10 mM**.**

Sr.No.	Oxime	Medium	pK_a	p$K_{a,app}$ (in presence of surfactants) [b]		
				12-4-12	16-10-16	SDS
1.	**4-PyC8**	Water	8.08	8.21	8.22	8.93
2.	**4-PyAlaC8**	25% (v/v) Ethanol-Water	8.12	8.27	8.24	8.82
3**.**	**4-PyPheC8**	25% (v/v) Ethanol- water	8.48	8.21	8.25	9.25
4.	**3-PyPheC8**	25% (v/v) Ethanol- water	9.00	-	9.21	-
5**.**	**2-PyPheC8**	25% (v/v) Ethanol- water	7.89	8.01	7.98	9.40
6.	**2-PAM**	Water (1M KCl)	8.04 + 0.05[a]	-	-	-
7.	**3-PAM**	Water (1M KCl)	8.61 + 0.04[a]	-	-	-
8.	**4-PAM**	Water (1M KCl)	9.51 + 0.06[a]	-	-	-

Notes: [a] - ref. [28, 75]; [b] water; CMC of 12-4-12, 16-10-16 and SDS reported in literature are 1.17 mM [76], 0.051 mM [77] and 8.2 mM [78], correspondingly

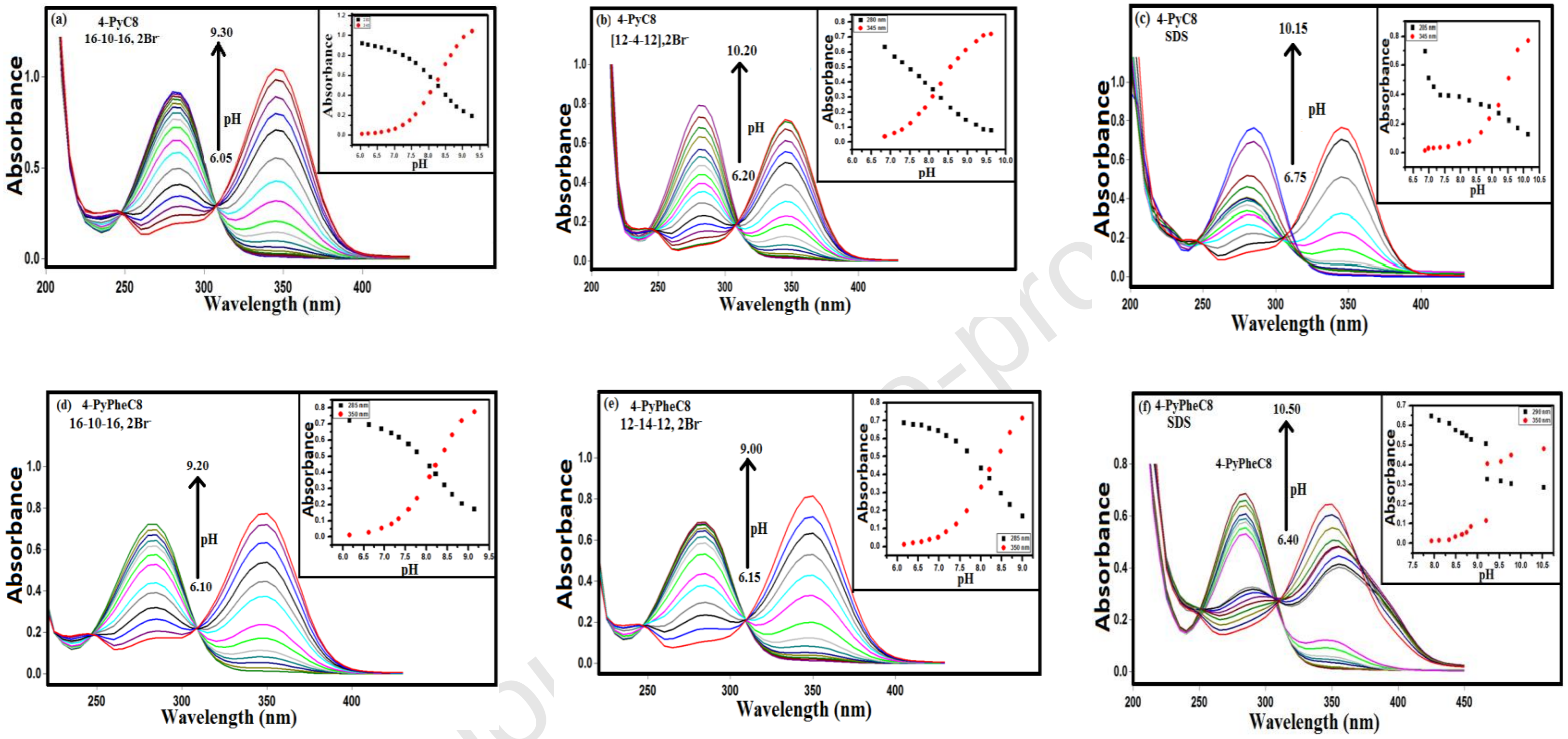
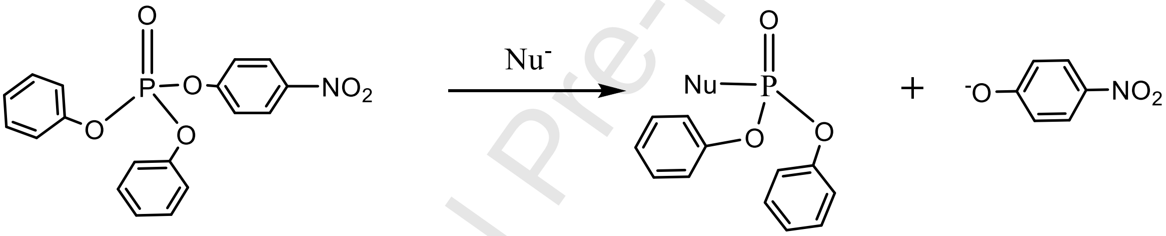


Fig. 4. Absorbance spectra of mixtures of IL-derived oximes (*a* – *c*, **4-PyC8**; *d* – *f*, **4-PyAlaC8**) with gemini surfactants 16-10-16 and 12-4-12, and anionic surfactant SDS. $[\text{Oxime}]_0$ =50 mM; $[\text{D}]_0$= 10 mM; 27 °C. Inset: Plots of absorbance *vs* pH for studied oximes in micellar solution.

4. Effect on cleavage of PNPDPP

The main expected advantages of low toxicity/biodegradable functional surfactant systems is an opportunity to ensure environmentally benign decontamination. PNPDPP is a phosphotriester which has been widely recruited as a stimulant (surrogate) and its hydrolytic reactions have been investigated [30, 38, 79, 80], see Scheme 6. Since PNPDPP is water insoluble, microheterogenerous (micellar, in essence) systems have been generally enroll as a reaction mechanism for the cleavage of PNPDPP. In such a medium, the organic reactants are partitioned into the surfactant aggregates by electrostatic and hydrophobic interactions. The observed rate assistance occurs mainly due to the increased localization of the reactants as well as the typical physical chemical properties of the micellar environment, which is remarkably different from those of the bulk solvents.



Scheme 6. Nucleophilic attack at phosphorus atom of PNPDPP

The **4-PyC8** was taken to estimate the reactivity in process of OP cleavage. In order to determine the efficiency of IL-derived oxime **4-PyC8** in decomposition of PNPDPP, kinetic studies have been performed at two different pH. The first-order rate constants been determined at pH 8.35 and 9.00, see Fig. 5. The nucleophilic concentration dependent first-order rate constants were determined spectrophotometrically for the reaction of PNPDPP with oxime in excess (Table 3; Scheme 6). The rate constant increases in both the concentration of nucleophilie and pH of the system. The obtained kinetic data entirely supports the hypothesis that oximate ion acting as a reactive species and possesses its α-effect properties. The observed reaction rates at pH 9.0 are substantially higher than reported in our previous study [38] for all oxime-functionalized surfactants (N-alkylated oximino pyridinium salts with C10 to C14 side chain), and comparable (but still higher, 0.0177 s^{-1} *vs* 0.0162 s^{-1}) to cetyl derivative.

Table 3. Hydrolysis of *p*-nitrophenyl diphenyl phosphate (PNPDPP) in the presence of **4-PyC8**. Reaction condition: [PNPDPP] = 0.5 mM; 27 °C.

		$10^3\,k_{obs}$, (s^{-1})	
		pH	
Sr. No.	**[D] mM**	**8.37**	**9.00**
1.	0	0.76	5.72
2.	0.5	2.57	9.27
3.	1.0	5.44	13.30
4.	3.0	11.10	17.70
5.	5.0	9.67	15.90

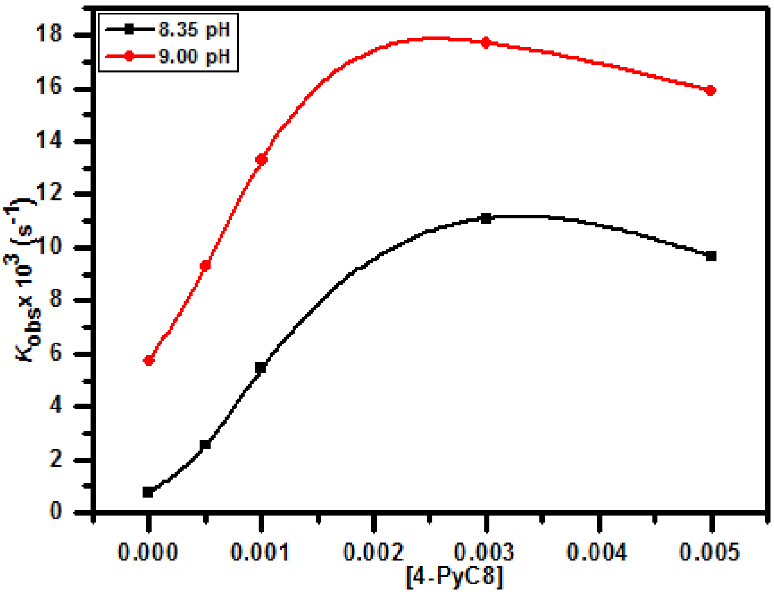


Fig. 5. Observed pseudo-first order rate constants (k_{obs}, s^{-1}) *vs*. [**4-PyC8**]$_0$ for reaction of PNPDPP cleavage; water, 27 ℃; [PNPDPP] = 0.5 mM.

Taking into account binding constant K_S of PNPDPP, a very hydrophobic OP substrate to be ≥ 10^4 M^{-1} [37], the second-order rate constant can be estimated from k_{obs} according to Eq. 6

$$k_{obs,\max} \cong (k_2^{'}/V_m) = (k_2^{m}/V_m)\cdot\alpha \qquad (6)$$

where k_2^m, M^{-1} s^{-1} is the second-order rate constant characterizing the nucleophilicity of the oximate fragment, V_m, M^{-1} is the partial molar volume of surfactant, which for this type of surfactants usually 0.4 M^{-1}, α – degree of deprotonation of the nucleophilic moiety. With the parameter α equal to 0.66 and 0.89 at pH 8.4 and 9.0, correspondingly, the k_2^{m} values can be calculated from kinetic data, which gives the values of 6.7 M^{-1} s^{-1} (pH 8.4) and 7.9 M^{-1} s^{-1} (pH 9.0) M^{-1} s^{-1}.

The practical procedure of chemical decontamination requires the smallest time possible for detoxification of an agent. The half-life times for oxymolysis of PNPDPP in optimal concentration conditions of [**4-PyC8**] calculated from the kinetic data (Table 3) are found to be ca. 62 s (pH 8.37) and ca. 40 s (pH 9.00), respectively. The values testify this system is capable to cleave by half the model OP within one minute of less under mild experimental conditions.

4. Conclusion

In this work, we presented synthesis of a series of novel IL-derived amphiphilic pyridinium oximes composed by octylamide tail linked to the headgroup by means of amide (**4-PyC8**), alanyl (**4-PyAlaC8**), or phenylalanyl (**2-PyPheC8**, **3-PyPheC8**, and **4-PyPheC8**) moiety. The biodegradability has been examined in the closed bottle test (CBT) to demonstrate that it is dependent on the amino acid structure and follows the tendency Phe> Ala> amide. Phe oximes demonstrate 34-39% of degradation in the CBT after 42 days and can be considered as inherently degradable. The acid ionization constant (pK_a) of studied oximes determined by means of UV-vis spectroscopy at 27 ° C were found to be in the range from 8.00 to 9.00. The $pK_{a,app}$ of studied oximes changes insignificantly in the presence of cationic gemini surfactants, 12-4-12- and 16-10-16, and shifted upwards in the presence of anionic surfactant SDS. The oxymolysis of OP triester PNPDPP under optimal concentration conditions of **4-PyC8** occurs with half-life times ca. 62 s and ca. 40 s at pH 8.37 and 9.00, respectively. Therefore, by means of nucleophilic attack of the alpha effect nucleophile, this IL-derives oxime system can provide cleavage one half of the model OP within one minute of less under mild experimental conditions. Results of this study can be useful in developing green and biodegradable compounds for chemical decontamination systems.

Acknowledgment

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AUTHOR'S STATERMENT

SJP - primary contribution into physico-chemical studies of the novel functionalized ILs: acid-base equilibria (including recording, interpretation, and discussion of the UV spectra), mixed systems, chemical kinetics; result interpretation and discussion, preparation of the preliminary report and the first draft of the manuscript.

IVK: overall contributed equally to the SJP; synthesis and complete characterisation of the all compounds used in the current study, running and analysis of the NMR spectra and preparation of the ESI; discussion of the results obtained and contribution into the development of the idea of the manuscript; contribution manuscript preparation (Experimental part and Results and discussion) on the all stages.

ZU: performing biodegradability studies via CBT – planning, sample preparation, running the experiment, data treatment and discussion; co-participation in the preparation of ESI and the final manuscript version.

RS and DS: participation in the physico-chemical studies of the novel compounds, including sample preparation containing mixed micelle system with gemini surfactants and an anionic surfactant determination of the pK_a values in the mixed micellar systems, oximolysis of the CWA simulant (PNPDPP) in the presents of the oxime IL.

NG: development of the idea, contribution into the planning of the biodegradability experiment and the projects topic related to the green chemistry issues, analysis and discussion of the data and contribution into the writing the manuscript; extended decisive work on the improvement of the language of the final version of the manuscript on the stage of its resubmission.

KKG: development of the idea, supervision over the physico-chemical experiments running, results discussion, contribution into the writing the manuscript on the all stages; one of the person for correspondence.

YK: conceived of the presented idea, development and coordination of the synthesis and planning and coordination of the studies of the novel compounds, overall results discussion, manuscript preparation with the primary help of SP and IK, and under support of NG, manuscript submission.

Declaration of interests

☒ The authors Subhashree Jayesh Pandya, Illia V. Kapitanov, Zeba Usmani, Reshma, Deepak Sinha, Nicholas Gathergood, Kallol K. Ghosh, and Yevgen Karpichev declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

On behalf

Research Highlights

- A series of novel amphiphilic oximes has been synthesized
- Oximes derived from Phe-ILs are inherently biodegradable
- The pK_a values of oximes are estimated to be 7.89 to 9.00
- Half-life of PNPDPP in the presence of IL-derived oxime is ≤ 1 min