

PYRYLIUM SALTS WITH LONG ALKYL SUBSTITUENTS AND DERIVED PYRIDINIUM SALTS*

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N-Phenylpyridinium chlorides with long alkyl substituents were prepared in high yields, using a macroporous, strongly basic, styrene-divinylbenzene anion exchange resin. All new compounds were characterized by ¹H- and ¹³C-NMR (at 400 MHz for proton and 100 MHz for carbon), IR and elemental analysis.

We have examined the surfactant properties of *N*-phenylpyridinium chlorides **1CI-4CI** and the relationship CMC vs number of carbon atoms of alkyl side chains for these new compounds.

INTRODUCTION

In the previous paper we described the synthesis and surfactant properties of pyridinium perchlorates with long alkyl substituents having a free ethyleneamino terminal group.¹

Heterocyclic compounds derived from pyridinium salts with long alkyl substituents are important chemicals having applications as ligands,² corrosion inhibitors,^{3,4} surfactants.⁵ They are cationic amphiphiles and have been recently investigated in connection with DNA trafficking into living cells.⁶

The first synthesis of pyrylium salts was reported by A.T. Balaban and C.D. Nenitescu.⁷

Over the past two decades, pyrylium salts with long alkyl substituents and derived pyridinium salts have been extensively studied in our laboratory. The Balaban-Nenitescu route has been applied to the synthesis of many 2,4,6-tri and

2,3,4,6-tetrasubstituted pyrylium and pyridinium salts with different substituents.⁸⁻¹⁵

In a previous paper, the preparation of new 1,2,4,6-tetrasubstituted and 1,2,3,4,6-pentasubstituted pyridinium chlorides having two different linear and long side chains in the 1,2- or 2,6-positions were described. An experimental procedure, spectral data and elemental analyses for all new compounds have been presented.¹⁶

We present here a new class of surfactants derived from pyridinium salts with long alkyl substituents. The synthetic procedure consists in conversion of pyridinium perchlorates to the corresponding chlorides. Our pyridinium surfactants differ from the ones described previously by the fact that they have a bulky phenyl substituent at the nitrogen atom.

As previous studies for other pyridinium chlorides have shown quite promising transfection efficiencies and low toxicities,⁶ these new compounds might be potential surfactants and transfection vectors.

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RESULTS AND DISCUSSION

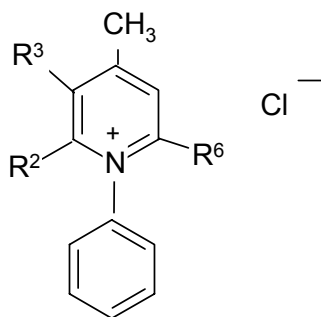
Materials and Methods

In previous papers,⁸⁻¹⁶ we reported the synthesis and the chromatographic separation of the complex acylation mixture yielding the pure pyrylium salts.

Two methods were employed for the conversion into pyridinium salts: either the direct

reaction of pyrylium salts with amine in boiling alcohol, or the reaction optimized by Katritzky at room temperature in methylene chloride. The pyridinium salts **1** – **4** were obtained by reaction between pyrylium salts and aniline.^{8, 11-14}

Figure 1 presents the new compounds described in this paper.



1Cl - 4Cl

Cpd.	R ²	R ³	R ⁶
1Cl	CH ₃	H	C ₁₁ H ₂₃
2Cl	C ₅ H ₁₁	H	C ₅ H ₁₁
3Cl	C ₁₁ H ₂₃	H	C ₁₁ H ₂₃
4Cl	C ₁₁ H ₂₃	CH ₃	C ₁₁ H ₂₃

Fig. 1 – The *N*-phenylpyridinium chlorides with long alkyl substituents.

All new compounds were characterized by ¹H- and ¹³C-NMR (at 400 MHz for proton and at 100 MHz for carbon), by IR spectra and by elemental analysis.

In previous papers,¹⁶ we reported the conversion of *N*-alkylpyridinium perchlorate with long alkyl substituents into the corresponding chlorides in quantitative yields, using a macroporous, strongly basic, anion exchange resin of styrene-divinylbenzene type. This procedure was successfully used for the *N*-phenylpyridinium chlorides **1Cl** - **4Cl** as well. These new compounds were characterized by elemental analyses, IR, UV-Vis, and NMR spectra. The surfactant properties and Critical Micellar Concentrations (CMC) determinations are also presented.

Scheme 1 presents the synthesis of the new compounds.

The conversion of pyridinium perchlorates **1** - **4** was easily performed by passing the perchlorate salts through the strongly basic ion exchange resin Vionit AT14 which was brought in the chloride

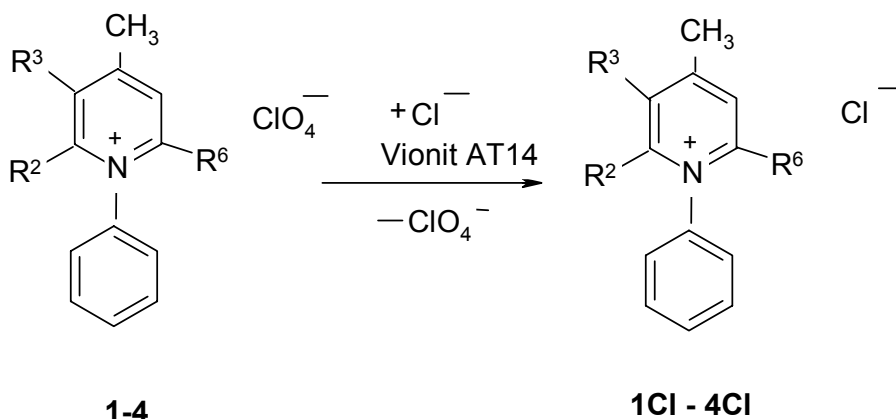
form in order to afford the chloride salts **1Cl** - **4Cl** in quantitative yields. All chloride compounds are waxy oils. Two solvent mixtures were useful for the anion exchange to pyridinium chlorides (methanol: water and acetone : water). The influence of the solvent and water concentration on the yield in pyridinium chloride is presented in Table 1. In all cases the use of a methanol: water mixture gave less satisfactory results. The mixture acetone: water as elution solvent gave the best results. The decrease in conversion into chlorides with increasing water concentration is due to the differences between the polarity of the solvent and pyridinium solubility. These results are consistent with our previously reported data.

The ¹H and ¹³C-NMR chemical shifts and IR results of pyridinium chlorides **1Cl** - **4Cl** were in agreement with the previously reported data.

Most of the signals for **1Cl-4Cl** were similar to those observed for the analogous perchlorates **1-4**. A small systematic difference in chemical shifts values for the β protons (3H/5H) of the pyridinium

salts, for the protons of *N*-phenyl and the alkyl side chain protons adjacent to the heterocyclic ring was observed (see Table 2). Comparison of the spectral data for **1Cl** - **4Cl** and **1** - **4** indicates that the different anion charge was responsible for differences in the ¹H-NMR spectra and this could be used to quantify the mixtures with partially exchanged anions. The chloride anion leads to slightly more deshielded signals than the

perchlorate. The ¹³C-NMR spectra of pyridinium chlorides **1Cl** - **4Cl** are summarized in Table 2 where only those signals which could be safely assigned are listed. For all these compounds, similar spectra to those observed for the analogous perchlorates were obtained.



Scheme 1 – The synthesis of **1Cl** – **4Cl**.

The only difference observed in the IR spectra was the absence of the broad and intense band at 1100 cm^{-1} which corresponds to the ClO_4^- anion.

Surfactant properties

The UV-VIS spectroscopy is a convenient method with good reproducibility for the determination of CMC of surfactants.¹⁷⁻¹⁹

On the other hand, it was shown that many pyridinium salts with long alkyl substituents have or are expected to have surfactant properties.^{5,20}

The first example of determination of critical micellar concentration (CMC) for pyridinium salts with different long chain substituents using UV-Vis spectroscopy at 20°C was reported recently.¹ A similar procedure was useful for compounds **1Cl** - **4Cl**, which have an *N*-phenyl group.

In order to obtain the diagrams absorbances vs concentration for CMC determination, the mixtures **1Cl** - **4Cl** / ethanol were prepared and allowed to stand at 20°C for one day. By measuring absorbance as a function of amphiphiles concentration, one can estimate its CMC from intercept of two straight lines (for similar determinations see ref.^{1,17}). By using such methods

for compounds **1Cl** - **4Cl** which contain a bulky phenyl substituent at the nitrogen atom, two critical concentrations (CMC and CC1) are estimated. The results are presented in Table 3.

We reported previously a classical CMC determination for *N*-ethyleneaminopyridinium perchlorate which have only one critical concentration. The opposite effect is evidenced by the *N*-phenyl substituent. For compounds **1Cl** - **4Cl**, on one hand, the *N*-phenyl substituent has a different effect probably because of its bulkiness preventing the favourable interaction of the α -alkyl side chains and on the other hand, the chloride anion determines a self-assembly micelles process at higher critical concentration (CC1).

One long chain substituent as in **1Cl** or two short carbon chains as in **2Cl** lead to relatively close values of the CMC. A second long chain as in **3Cl** and **4Cl** decreases significantly the CMC/CC1 values (see Table 3).

For all new compounds, according to the well-known data, the CMC and CC1 decreases with the increase in both the number of substituents and the length of the hydrophobic alkyl groups.^{1,21}

Table 1

Conversion of *N*-alkylpyridinium perchlorates into *N*-alkylpyridinium chlorides^a

Cpd	Mol. Form.	E.A. (%)		Aspect ^b	m.p. (°C)	Synthesis Solvent	Solvents Ion Exchange	Vol:Vol	Product	ClO ₄ /Cl ^c	Yield (%)
		Calcd.	Found								
1	C ₂₄ H ₃₆ NCIO ₄	N:3.19 Cl:8.11	N:3.09 Cl:8.12	CC	WO CR	C ₂ H ₅ OH	-		-		
1Cl	C ₂₄ H ₃₆ NCl	N:3.75 Cl:9.50	N:3.73 Cl:9.60	WO CR	WO CR	-	(CH ₃) ₂ CO:H ₂ O	85:5	1Cl	-	99 ^d
							(CH ₃) ₂ CO:H ₂ O	70:10	mixture of 1 and 1Cl	1:1	50 ^e
							CH ₃ OH:H ₂ O	65:5	Complex mixture ^f	1:3	35 ^e
2	C ₂₂ H ₃₄ NCIO ₄	N:2.37 Cl:6.00	N:2.48 Cl:6.18	WO CR	26	CH ₂ Cl ₂	-		-		
2Cl	C ₂₂ H ₃₄ NCl	N:2.65 Cl:6.73	N:2.69 Cl:6.83	Waxy oil	WO CR	-	(CH ₃) ₂ CO:H ₂ O	85:5	2Cl	-	99 ^d
							(CH ₃) ₂ CO:H ₂ O	70:10	mixture of 2 and 2Cl	1:1	50 ^e
							CH ₃ OH:H ₂ O	65:5	Complex mixture ^f	1:2	25 ^e
3	C ₃₄ H ₅₆ NCIO ₄	N:2.42 Cl:6.15	N:2.72 Cl:6.12	CC	84.5-85	C ₂ H ₅ OH	-		-		
3Cl	C ₃₄ H ₅₆ NCl	N:2.73 Cl:6.91	N:2.83 Cl:6.95	WO CR	-	-	(CH ₃) ₂ CO:H ₂ O	70:5	3Cl	-	99 ^d
							(CH ₃) ₂ CO:H ₂ O	60:10	mixture of 3 and 3Cl	2:1	40 ^e
							CH ₃ OH:H ₂ O	65:5	Complex mixture ^f	3:1	20 ^e
4	C ₃₅ H ₅₈ NCIO ₄	N:2.37 Cl:6.00	N:2.45 Cl:6.10	WO CR	18	CH ₂ Cl ₂	-		-		
4Cl	C ₃₅ H ₅₈ NCl	N:2.65 Cl:6.73	N:2.68 Cl:6.72	Waxy oil	-	-	(CH ₃) ₂ CO:H ₂ O	80:5	4Cl	-	99 ^d
							(CH ₃) ₂ CO:H ₂ O	70:10	mixture of 4 and 4Cl	1:1.5	54 ^e
							CH ₃ OH:H ₂ O	65:5	Complex mixture ^f	2:1	35 ^e

^a All reactions were performed at 25°C using Vionit AT14; ^b CC stands for Colorless Crystals while WO CR stands for Waxy Oil which Crystallized in the Refrigerator (4 °C); ^c Determined by ¹H-NMR (400 MHz) analysis; ^d Analytically pure compound; ^e Determined after preparative TLC purification; ^f mixture of **1-4** with corresponding **1Cl-4Cl** and ring opened products (see ¹⁶).

Table 2

Selected signal assignments for $^1\text{H-NMR}$ spectra (400.13 MHz) and for $^{13}\text{C-NMR}$ (100.61 MHz) of **14** and **14Cl**

Cpd.	C-2	C-4	C-6	C-5	C-3	2CH ₃	3CH ₃	4CH ₃	2 ₂ 'CH ₂	2 ₆ 'CH ₂	3'CH ₂	1''	2'',6''	3'',5''	4''
1	-/ 177.65	-/ 174.58	-/ 180.84	7.65/ 124.26	7.57/ 122.78	2.39/ 22.36	-	2.73/ 22.71	2.54/ 34.02	-	1.59/ 28.64	-/ 137.93	7.44/ 126.09	7.67/ 131.76	7.67/ 131.75
1cl	-/ 177.87	-/ 174.60	-/ 181.22	7.68/ 124.88	7.59/ 122.80	2.47/ 22.56	-	2.73/ 22.73	2.81/ 34.33	-	1.61/ 28.70	-/ 137.99	7.48/ 126.19	7.70/ 131.78	7.71/ 131.77
2	-/ 157.21	-/ 159.42	-	-	7.65/ 126.09	-	-	2.59/ 22.15	2.49/ 34.25	-	1.53/ 26.94	-/ 135.87	7.59/ 125.80	7.67/ 131.18	7.67/ 131.28
2cl	-/ 157.31	-/ 159.52	-	-	7.67/ 125.99	-	-	2.59/ 22.19	2.53/ 34.99	-	1.54/ 26.97	-/ 135.99	7.61/ 125.85	7.69/ 131.28	7.68/ 131.30
3	-/ 157.99	-/ 159.62	-	-	7.55/ 126.40	-	-	2.77/ 22.15	2.49/ 34.03	-	1.53/ 28.62	-/ 136.29	7.49/ 126.22	7.57/ 131.60	7.57/ 131.70
3cl	-/ 158.04	-/ 159.80	-	-	7.57/ 126.90	-	-	2.77/ 22.25	2.59/ 34.43	-	1.55/ 28.92	-/ 136.49	7.53/ 126.94	7.61/ 131.63	7.60/ 131.72
4	-/ 153.22	-/ 158.90	-/ 156.05	7.57/ 134.31	-/ 128.29	-	2.25/ 15.27	2.44/ 21.75	2.34/ 34.02	2.36/ 34.18	1.42/ 28.56	-/ 139.73	7.45/ 126.39	7.61/ 131.21	7.61/ 130.92
4cl	-/ 153.42	-/ 158.94	-/ 156.55	7.59/ 134.81	-/ 128.33	-	2.28/ 15.47	2.50/ 22.15	2.42/ 34.42	2.46/ 34.53	1.42/ 28.86	-/ 139.93	7.49/ 126.99	7.65/ 131.81	7.64/ 131.12

Table 3

Surfactant properties of **1CI-4CI**

Cpd.	λ (nm)	Number Cabon Atoms	CMC, mMx10 ⁻³	CC1, mMx10 ⁻²
1CI	242.20	24	32.5	22.1
2CI	242.20	22	39.8	87.0
3CI	242.20	34	2.03	9.15
4CI	245.95	35	0.6	8.16

EXPERIMENTAL PART

The NMR spectra have been recorded on a BRUKER AVANCE 400 DRX instrument, equipped with a 5 mm inverse detection multinuclear probehead and field gradients on the z axis, operating at 400.13 MHz for ¹H and at 100.61 MHz for ¹³C nuclei. The COSY45, HMQC and HMBC spectra have been recorded with standard Bruker parameters in the versions employing pulsed field gradients. All spectra have been recorded in deuterated chloroform, and the chemical shifts have been reported as δ values referenced to TMS as an internal standard. Infrared spectra were run on a BRUKER VERTEX 70 instrument equipped with a Golden Gate diamond ATR. The UV-VIS spectra were recorded with a GBC type 918 instrument in 1 cm cuvettes. Melting points were measured in open capillary tubes (for the low melting compounds) or on a hot-stage melting points apparatus (equipped with a polarizer to check for nematic properties).

Conversion of *N*-phenyl-pyridinium perchlorates 1-4 into *N*-phenyl-pyridinium chlorides 1CI-4CI. General Procedure

Vionit AT14 - chloride (0.3-1.25 mm, 1.5-2 g) was slurried with aqueous HCl 6% (use of deionized water is recommended) and packed into an usual chromatography column. The resin was washed with 6% HCl until the effluent was clear (4-5 bed volumes), deionized water until the pH increased to 7 (4-6 bed volumes), and finally with an acetone / water mixture (70:5-85:5 vol/vol). The perchlorate salts (0.1-0.2 mmol) dissolved in acetone / water (10:1) were loaded in the column and eluted with acetone/water (70:5-85:5 vol/vol). The appropriate fractions were evaporated and the resulting solid further dried in a vacuum oven. Elemental analyses for the chloride salts were consistent with a successful ion exchange.

Surfactant properties

In order to obtain the diagrams absorbances vs concentration for CMC determination, the mixtures **1CI - 4CI** / ethanol were prepared and allowed to stand at 20°C for one day. The UV-Vis spectra were recorded with a GBC type 918 instrument in 1 cm cuvettes.

The representation of the absorption at a fixed wavelength and temperature for various concentrations of amphiphiles showed several lines from experimental points which intersect in this case first at the CMC value and second at the CC1 value (see ¹).

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