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Synthesis and physico-chemical properties of a novel series of aromatic electron acceptors based on *N*-heterocycles

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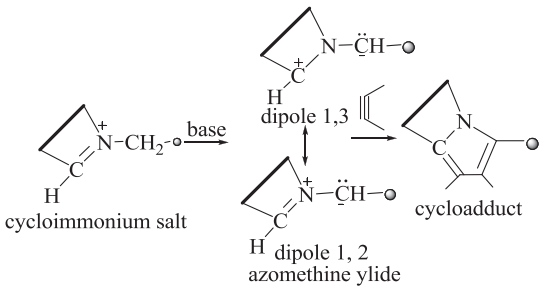
ABSTRACT

The synthesis of a novel series of N-based heterocyclic salts using a simple and efficient N-alkylation of 1,2-bis(4-pyridyl)ethane with reactive halides is reported. These compounds can be transformed into the corresponding pyridinium methylides by addition of a base. The former exhibit an unstable absorption bands at 395–410 nm. The structures of the salts were fully characterized by UV–vis, IR, NMR and MS spectroscopy and elemental analysis. The *pK* values of selected compounds were also determined and the acid–basic equilibrium was investigated by UV–vis spectrophotometry. The thermal stability of all species was determined by thermogravimetric analysis.

1. Introduction

Pyridinium quaternary salts are a versatile class of compounds having a wide range of interesting properties and continuing to receive an increasing attention.[1–10] This is mainly because they can be easily functionalized at the nitrogen heterocyclic atom in order to obtain useful species for biological and industrial applications,[1–16] for example, cosmetics, pharmaceuticals, gene delivery and polymerization.[4,5] Moreover, pyridinium salts attract the attention of scientists because they can be employed as electron carriers, model systems in photosynthesis, cardiovascular agents, hypotensive, neuromuscular agents,[6,7] and they are also effective as phase transfer agents and catalyst, initiators of cationic polymerization, acylating agents,[8,9] wide range antimicrobials,[1,2,10,16] enzyme inhibitors,[11] dyes,[12] and cationic surfactants.[14] Selected salts were also found to be ionic liquids[15] whereas others named viologens (4,4′-bipyridinium salts) demonstrate electrochromic properties.[17]

Pyridinium salts can also be transformed in their corresponding pyridinium ylides, nucleophilic 'zwitterionic' structures, by addition of a base. This property is important for the synthesis of new heterocyclic compounds by dipolar cycloaddition (Scheme 1).[18] The ylides are coloured compounds, which in acidic condition became colourless due to their transformation into the corresponding salts.[19]



Scheme 1. Ylide formation in basic conditions.

Following our interest in the synthesis of N-base quaternary salts that can be used as precursors for obtaining, through cycloaddition reactions, fluorescent or antimicrobial indolizine compounds,[20–23] we describe here the synthesis and characterization of a new series of quaternary pyridinium salts, based on 1,2-bis(4-pyridyl)ethane, a molecule containing three distinct parts: a flexible unit, a rigid polarisable aromatic core, and a positively charged pyridinium ring associated to a negatively charged counterion. In order to apply these species in the fields above described we have also decided to measure their dissociation constants (*pK*a) that gives information on the chemical reactivity, salt

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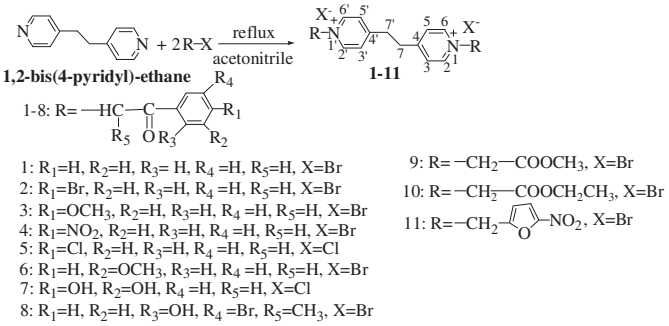
formation and chromatographic separation, and to study the thermal stability by TGA that informs about the temperature range where the investigated compounds may be used and stored.

2. Results and discussions

2.1. Synthesis

The synthesis of the quaternary pyridinium salts **1**–**11** (Scheme 2) derived from 1,2-bis(4-pyridyl)ethane has been carried through the alkylation of 1,2-bis(4-pyridyl)ethane by reactive halogenated derivatives in anhydrous solvents, which seems to be the most convenient method between those reported in literature.[4,11–13] The structure of **1**–**11** has been assigned on the basis of IR, ^{1}H NMR and ^{13}C NMR spectroscopy, MS and elemental analysis, while its purity was confirmed by HPLC.



Scheme 2. Synthesis of diquaternary salts of bis(pyridinium).

The IR spectra of the pyridinium salts **1**–**11** show characteristic bands in the following range: 3040–3000 cm^{-1} (νCH$_{arom.}$), 2900–2880 cm^{-1} (νCH$_{aliph}$), 1730–1722 cm^{-1} (νC=O$_{ester}$), 1700–1670 cm^{-1} (νC=O), 1640–1630 cm^{-1} (νC=N), 1530 and 1350 cm^{-1} (νNO$_2$), 1200 and 1100 cm^{-1} (νC–O–C) and ~990 cm^{-1} (C–C$_{aliph}$). The molecular structures of **1**–**11** were further confirmed by ^{1}H NMR spectroscopic analysis. All these compounds show multiple peaks in the region of 9.10–7.20 ppm, which can be assigned to aromatic protons. Additionally, the characteristic peaks at 6.66–5.67 ppm can be attributed to the CH$_2$ or CH close to the cationic nitrogen whereas the peak centred at 3.39–3.54 ppm is due to the bridging CH$_2$. Also, it is evident that the protons from the pyridinium rings are shifted to the low field when compared with 1,2-bis(4-pyridyl) ethane (Table 1). The ^{13}C NMR spectra also confirm the synthesised structures. Thus, for compounds **1**–**8** at 188–195 ppm appear the signals of the quaternary carbon of carbonyl groups, while the signals of the ester carbonyl groups for compounds **9**, **10** appear at 166 ppm. At high fields (~56–73 ppm) we found the signals for CH$_2$ or CH groups close to the pyridinium nitrogen, whereas the signals from 33 to 35 ppm can be attributed to carbons of the bridging CH$_2$ groups.

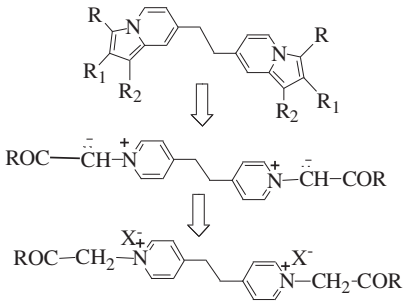
Due to the ionic structure of the synthesized compounds, their electrospray mass spectra (ESI-MS) have a major peak for the signal of organic ions [M^{2+}–H$^+$], with masses between 329 and 639, where M^{2+} represents the mass of the organic skeleton from the diquaternary salt molecules.

2.2. Determination of acid dissociation constants of diquaternary salts

As mentioned above, we are interested in the use of the 1,2-bis(4-pyridyl)ethane diquaternary salts as synthons in cycloaddition reactions to obtain fluorescent indolizines (Scheme 3). Important information concerning the salts tendency to form the corresponding ylides, by deprotonation in basic medium, could be obtained by determination of their pk_a values. According to Ratts and co-workers,[24] the pK_a values of diquaternary salts could be used to estimate the nucleophilicity and hence reactivity of the corresponding ylides. Thus, the lower the salt pK_a value, the lower the ylide basicity and the higher its stability.

Table 1
Selected ^{1}H NMR data of compound **1**–**11** and 1,2-bis(4-pyridyl)ethane

Compound	^{1}H NMR δ (DMSO-d_6)		
	H-7, H-7′-	H-2, H-2′ H-6, H-6′	H-3, H-3′ H-5, H-5′
1,2-bis(4-pyridyl) ethane	2.93 (s,4H)	8.51–8.57(dd, 4H)	7.072–7.083 (dd, 4H)
1	3.50 (s,4H)	8.96 (d, 4H)	8.27 (d, 4H)
2	3.48 (s,4H)	8.91 (d, 4H)	8.24 (d, 4H)
3	3.54 (s,4H)	8.95 (d, 4H)	8.26 (d, 4H)
4	3.51 (s,4H)	8.96 (d, 4H)	8.49 (d, 4H)
5	3.47 (s,4H)	8.93 (d, 4H)	8.24 (d, 4H)
6	3.54 (s,4H)	8.95 (d, 4H)	8.26 (d, 4H)
7	3.45 (s,4H)	8.91(d, 4H)	8.20 (d, 4H)
8	3.45 (s,4H)	9.11 (d, 4H)	8.21 (d, 4H)
9	3.45 (s,4H)	9.00 (d, 4H)	8.23 (d, 4H)
10	3.45 (s,4H)	9.01 (d, 4H)	8.24 (d, 4H)
11	3.39 (s,4H)	9.10 (d, 4H)	8.17 (d, 4H)



Scheme 3. Retrosynthetic strategy for indolizine formation.

Thus, the acid dissociation constants (pK_a) of four synthesized 1,2-bis(4-pyridyl)ethane diquaternary salts **1**–**4** were determined from UV–vis spectrometric data, using the method of Albert and Sergeant.[25] The investigated products were chosen in order to afford some correlations between the acid–basic equilibrium and salt's structures.

The method is based on the direct determination of the ratio of non-dissociated (protonated, salt) to dissociated (deprotonated, ylide) species in a series of non-absorbing buffer solutions. First the spectra of protonated and deprotonated molecules were obtained in an acid (hydrochloric acid) and in an alkali (sodium hydroxide) solution, in which compounds of interest would be present in either form. Next, the absorption spectra of each of the analyzed compounds in ten non-absorbing Britton–Robinson buffer solutions, with pH ranging from 5.31 to 11.84, with a constant ionic strength maintained with sodium chloride, were measured. From the absorbtion spectra, a set of ten pK_a values were obtained using Eq. (1):

$$\mathrm{pKa} = \mathrm{pH} + \log[(\mathrm{Di} - D)/(D - \mathrm{Dm})] \quad (1)$$

where Dm and Di correspond to the optical density of protonated and deprotonated forms of compound, and D is the optical density in the buffer determined at analytical wave lengths.

The average value of the ten measurements was considered the pK_a of the diquaternary salt. The spectra used in spectrophotometric determination of pK_a value for salt **1** are reproduced in Fig. 1.