JOURNAL OF PHYSICAL ORGANIC CHEMISTRY
J. Phys. Org. Chem. **12,** 39–46 (1999)

Deprotonation of 1-(carbethoxyalkyl)pyridinium halides with strong N-bases

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Received 1 November 1997; revised 20 February 1998; accepted 16 March 1998

ABSTRACT: The rate constants were measured for deprotonation of 1-(carbethoxymethyl)pyridinium chloride and 1-(2-carbethoxyethyl)pyridinium bromide with strong bases (DBU, MTBD, TBD and P2-Et) in acetonitrile. The UV spectra and semiempirical calculations are consistent with an ylide structure of the deprotonated species. The ylides obtained slowly decompose, and the reaction products were identified by ^{1}H NMR spectroscopy; 1-(carbethoxymethyl)pyridinium chloride gives *N*-methylpyridinium cation and ethanol and 1-(2-carbethoxyethyl)pyridinium bromide converts to pyridine and ethyl acrylate. Copyright © 1999 John Wiley & Sons, Ltd.

KEYWORDS: carbethoxyalkylpyridinium halides; deprotonation; strong bases; ylide

INTRODUCTION

Strong bases can abstract either α- or *β*-protons from quaternary ammonium halides. Abstraction of an α-proton gives ylides as the intermediates. When a *β*-proton is removed, an elimination can occur that is similar to a Hofmann elimination.[1]

Most *N*-ylides are capable of only fleeting existence.[2] On the other hand, in pyridinium-type ylides a delocalization of charge into the heterocyclic ring may occur and the stability of such compounds is enhanced. Pyridine ylides with C = O or CN groups are so stable that their structures could be determined by x-ray diffraction.[3–6]

Ammonium ylides are important precursors in organic synthesis, owing to their rearrangement under mild conditions to form highly substituted organic compounds and the ability to prepare compounds stereospecifically from ammonium ylides.[7] The major drawback in the use of ammonium ylides in synthesis is the competition between the two primary rearrangement pathways of these compounds, the Stevens [1, 2] and the Sommelet–Hauser [2, 3] rearrangements.[7,8]

Pyridinium ylides without a *β*-hydrogen react with olefinic dipolarophiles.[9–11] The reactivity of the *N*-CH_2 group in carbethoxymethylpyridinium salts becomes comparable to that of the methylene groups in *β*-keto esters.[12] In these compounds, the action of base rapidly generates ylides and further reaction results in cleavage to an acid and an *N*-methylpyridinium salt,[13] by a mechanism probably similar to that involved in the fission of *β*-dicarbonyl compounds. In the case of ylides with a *β*-hydrogen, there is a possibility of Hofmann elimination to form an alkene and pyridine or a less substituted amine.[1]

Most alkene-forming elimination reactions proceed through a one-step concerted *E*2 mechanism or a stepwise *E*1*cB* mechanism with a carbanionic intermediate.[14] Bunting *et al.*[15] reported a detailed kinetic study of the hydroxide ion-catalysed elimination of pyridines from *N*-(2-cyanoethyl)pyridinium cations in aqueous solution for a pyridine group having a pK_{BH} in the range 1.5–9.7. Reaction rates are both pH and X-substituent dependent, with a total range of 4×10^5-fold in pseudo-first-order rate constants. Brønsted plots as a function of the basicity of the pyridine leaving group are concave-down, which is consistent with a change in rate-determining step within an *E*1*cB* mechanism. These plots are characterized by $\beta_{lg} = -0.30$ for the rate-determining deprotonation for $pK_{BH} < 5.8$ and $\beta_{lg} = -0.93$ for the rate-determining expulsion of the pyridine nucleofuge from the carbanionic intermediate for $pK_{BH} > 5.8$. These reactions are further perturbed by hydrogen–deuterium exchange and by the Michael-type addition of pyridines ($pK_{BH} > 6$) to acrylonitrile to produce *N*-(2-cyanoethyl)pyridinum cations.

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Email: szafran@main.amu.edu.pl
Contract/grant sponsor: Polish Committee for Scientific Research (KBN); *Contract/grant number:* 2P 303 06907.

CCC 0894–3230/99/010039–08 $17.50

In this work we investigated the deprotonation reactions of 1-(carbethoxymethyl)pyridinium chloride (**1a**) and 1-(2-carbethoxyethyl)pyridinium bromide (**2a**) by strong bases in aprotic solvents to obtain information on the relative acidity of hydrogens in methylene groups in the α- and β-positions.

RESULTS AND DISCUSSION

The strong N-bases 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) ($pK_a = 23.9$),[16] 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD) ($pK_a = 24.70$),[17] 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) ($pK_a = 24.97$)[17] and Schwesinger base, phosphazene (P2-Et) ($pK_a = 32.80$)[18] were used for deprotonation reactions; pK_a values were determined in acetonitrile solution (Scheme 1).

When a 1-(carbethoxyalkyl)pyridinium halide (AH) is treated with an excess of a strong base (B) ($[B_0] \gg [AH_0]$), the following processes can occur:

$$AH + B \underset{k_-}{\overset{k}{\rightleftharpoons}} (A^-, B^+H);\ k_{obs} = k[B_0] + k_- \qquad (1)$$

$$AH + B \underset{k_-}{\overset{k}{\rightleftharpoons}} A^- + B^+H;\ k_{obs} = k[B_0] + k_-[B^+H] \qquad (2)$$

$$AH + B \underset{k_-}{\overset{k}{\rightleftharpoons}} (A^-, B^+H) \overset{K_D}{\rightleftharpoons} A^- + B^+H;\ k_{obs} = k[B_0] + k_-[B^+H]/K_D \qquad (3)$$

where k is the rate constant for the deprotonation (forward) reaction, k_- is the rate constant for the protonation (backward) reaction, $[B_0]$ is the initial base concentration, $[B^+H]$ is the concentration of the cation and K_D is the dissociation constant of the ion pair (A^-, B^+H) (Scheme 2).

The k_{obs} values were calculated from the traces of absorbance (**1a**, 420 nm; **2a**, 368 nm) vs time and are listed in Tables 1 and 2. When k_{obs} is plotted vs $[B_0]$ an excellent straight line is obtained ($r > 0.99$), where the slope gives k values and the intercept k_- values (Tables 1 and Table 2). This indicates that Eqn (1) describes the investigated reaction properly. Note however that in the case of Eqn (2) the term $[B^+H]$ is not constant; the process for the forward reaction is first order but that for the backward reaction is second order.

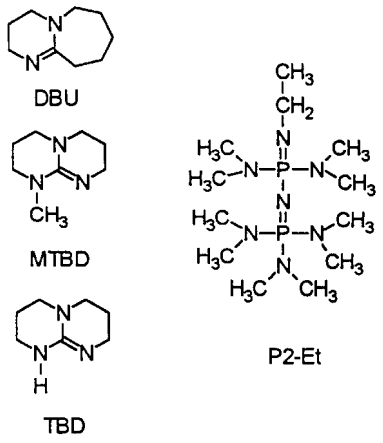
Although Eqn (1) correctly fits the experimental data model, Eqn (3) cannot be completely neglected. The dissociation of the hydrogen-bonded ion pairs into ions increases with increasing dilution and temperature. It seems that the contribution of solvated ions can be neglected in the range of concentration and temperature applied in this work.

In ylides the carbon is basic and acts as a hydrogen bond acceptor. According to *ab initio* calculations (MP2/6–311 + + G^{**}), ylides form hydrogen bonds even with such weak proton donors as methanol.[19]

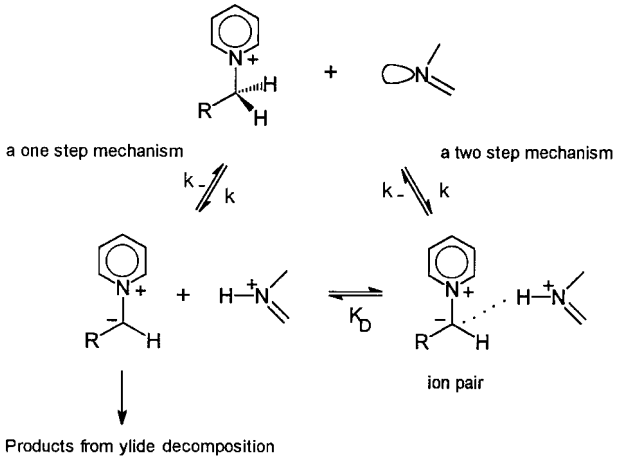
More reactive **1a** undergoes deprotonation with all bases in acetonitrile and DMSO solutions to give ylide **1b**. However, P2-Et, as the strongest base, reacts too fast to be investigated quantitatively (Table 1).

The activation parameters were calculated by the linear least-squares fit of ln$k$ vs $1/T$ (Table 3). The values of $\Delta G^{\neq}$ are independent of the N-base used, within experimental error. The large negative values for the entropy of activation ($\Delta S^{\neq}$) reveal that solvation in the transition state is highly ordered.

The deprotonation rate constants of **1a** are comparable to those for deprotonation of dimethyl (4-nitrophenyl)-



Scheme 1



Scheme 2

Table 1. Kinetic data (standard deviation in parentheses) for the deprotonation reaction of 1-(carbethoxymetyl)pyridinium chloride (**1a**) (3×10^{-5} M) with bases (0.0005–0.0075 M) in acetonitrile

		k_{obs} (s^{-1})					
Base	Temperature (°C)	0.0005 M	0.0025 M	0.0050 M	0.0075 M	10^{-4} k (l mol^{-1} s^{-1})	Int (s^{-1})
DBU	5	200 (3)	285 (4)	410 (5)	530 (7)	4.75 (9)	172 (5)
	10	285 (4)	402 (5)	535 (6)	673 (9)	5.51 (7)	260 (3)
	15	365 (5)	485 (3)	655 (8)	830 (12)	6.67 (15)	325 (7)
	20	500 (6)	640 (3)	835 (5)	1027 (11)	7.57 (13)	457 (5)
	25	615 (6)	774 (8)	986 (7)	1210 (12)	8.51 (15)	566 (7)
MTBD	5	230 (4)	336 (3)	480 (4)	630 (8)	5.76 (10)	197 (3)
	10	254 (3)	377 (6)	555 (8)	729 (9)	6.94 (7)	207 (3)
	15	260 (2)	413 (5)	608 (8)	810 (9)	7.86 (6)	218 (3)
	20	263 (5)	443 (5)	658 (11)	871 (10)	8.71 (9)	221 (4)
	25	285 (4)	480 (6)	726 (11)	986 (11)	10.27 (13)	216 (6)
TBD	5	263 (4)	421 (4)	642 (8)	856 (8)	8.52 (12)	215 (6)
	10	302 (5)	500 (5)	760 (10)	974 (9)	9.51 (28)	260 (13)
	15	342 (3)	557 (4)	827 (9)	1072 (13)	10.46 (17)	294 (8)
	20	389 (5)	621 (8)	897 (9)	1194 (11)	11.56 (13)	325 (6)
	25	430 (4)	675 (8)	1004 (11)	1320 (13)	12.77 (11)	366 (5)
P2-Et	— [a]						

[a] The reaction is too fast.

Table 2. Kinetic data (standard deviation in parentheses) for the deprotonation reaction of 1-(carbethoxyethyl)pyridinium bromide (**2a**) (3×10^{-5} M) with P2-Et (0.0005–0.0125 M) in acetonitrile

	k_{obs} (s^{-1})					
Temperature (°C)	0.0005 M	0.0075 M	0.0100 M	0.0125 M	k (l mol^{-1} s^{-1})	Int (s^{-1})
5	0.035 (2)	0.075 (2)	0.103 (5)	0.143 (3)	141 (7)	−0.030 (1)
10	0.053 (2)	0.100 (3)	0.135 (3)	0.186 (4)	174 (8)	−0.030 (1)
15	0.112 (4)	0.175 (4)	0.235 (4)	0.294 (4)	242 (8)	−0.030 (1)
20	0.173 (4)	0.254 (4)	0.341 (3)	0.425 (5)	337 (3)	0.003 (1)
25	0.250 (5)	0.362 (4)	0.485 (5)	0.611 (4)	474 (9)	0.010 (1)

Table 3. Thermodynamic data

Compound	Base	$\Delta H^{\neq}$ (kJ mol^{-1})	$-\Delta S^{\neq}$ (J mol^{-1} K^{-1})	$\Delta G^{\neq}$ (kJ mol^{-1})
1a	DBU	18.11 ± 0.90	90 ± 3	44.87 ± 0.90
	MTBD	16.71 ± 1.02	93 ± 4	44.47 ± 1.02
	TBD	11.24 ± 0.42	109 ± 2	43.91 ± 0.42
2a	P2-Et	40.12 ± 2.46	60 ± 8	57.89 ± 2.46

malonate.[20] This result conforms to that of compounds containing a CH_2 group flanked by two activating carbonyl substituents.

Figure 1 illustrates the UV spectrum of **1a** in acetonitrile and its time-dependent changes on addition of P2-Et. The absorption at 420 nm is a result of the resonance interactions of the ylide chromophore with the COOEt substituent (**1b** ⇋ **1c**) (Scheme 3). The significant decrease in intensity of the 420 nm absorption reflects conversion of the ylide to products as shown in Scheme 3. These reaction products were identified by ^{1}H NMR spectroscopy. For **1a** the reaction products have spectroscopic properties identical with those of a mixture of *N*-methylpyridinium iodide[21] and ethanol. The ^{1}H NMR chemical shifts of **1a**, its reaction mixture with P2-Et and the decomposition products of the ylide are listed in Table 4. When P2-Et is added to **1a**, the signals due to

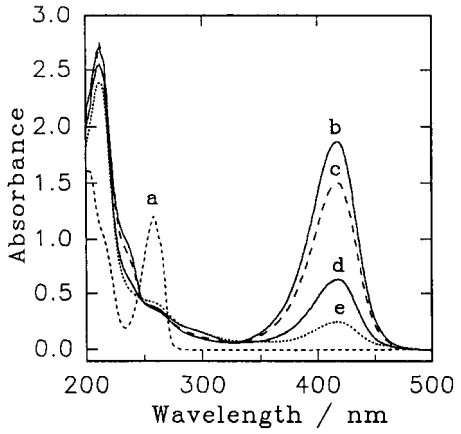
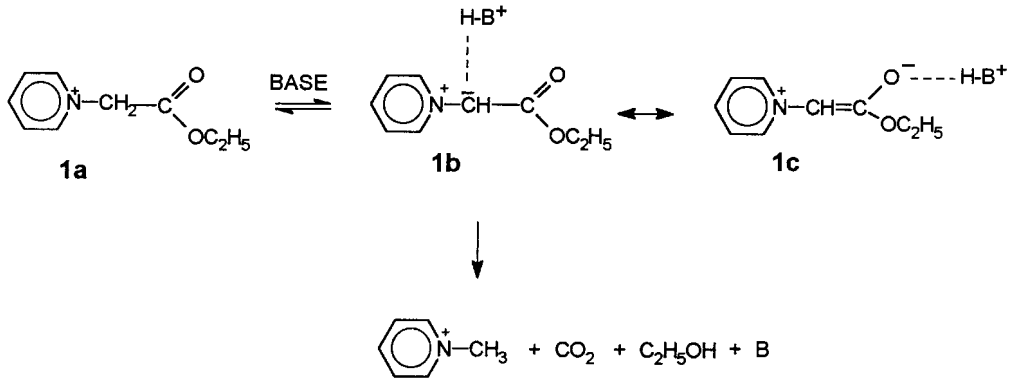
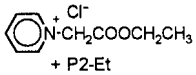
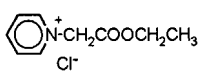
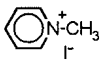


Figure 1. UV–visible spectra of (a) **1a** (5×10^{-5} M) and a mixture of **1a** (4×10^{-5} M) with P2-Et (1×10^{-2} M) in acetonitrile after (b) 0.5, (c) 6, (d) 12 and (e) 20 min



Scheme 3

Table 4. ^{1}H NMR data for products resulting from the reaction between **1a** and P2-Et in DMSO-d_6[a]

Assignment		 + P2-Et		P2-Et		CH_3CH_2OH
H_α	a	9.33(broad)	9.29(d)	—		—
	b	8.98(d)			9.00(d)[b]	
H_β	c	8.28(broad)	8.30(t)	—		—
	d	8.11(t)			8.12(t)[b]	
H_γ	e	8.75(broad)	8.75(t)	—		—
	f	8.57(t)			8.57(t)[b]	
N-CH_2	g	5.96(broad)	5.93(s)		—	—
	h	2.80(m)		2.80(m)		
N-CH_3	i	2.64(s)	—	2.61(s)		—
	j	2.63(s)		2.58(s)		
	k	2.61(s)		2.54(s)		
	l	2.60(s)		2.50(s)		
	m	2.52(s)				
	n	5.02(s)			4.37(s)[b]	
OCH_2	o	4.21(d, broad)	4.24(q)	—	—	
	p	3.44(q)				3.44(q)
CH_3	r	1.24(t)	1.29(t)		—	
	s	1.09(t)		0.95		
	t	1.05(t)				1.05(t)

[a] d = Doublet; m = multiplet; t = triplet; q = quartet.
[b] Data from Ref. 21.

the protons of the pyridine ring lost their multiplicity and become broad (Fig. 2). This suggests that **1a** is in a dynamic equilibrium with **1b** and **1c**.

Deprotonation of the less reactive species, **2a**, was investigated only with P2-Et (Table 2), because the reaction with other bases was too slow to study. In **2a** there are two CH_2 groups and their relative acidities are not known. One may expect that the formation of the ylide **2b** would produce a considerable red shift and hyperchromic effect in the UV spectra because of lengthening of the conjugated system. On the other hand, the formation of **2c** would cause little change in the absorption. As Fig. 3 shows, addition of P2-Et to **2a** shifts the absorption to *ca* 368 nm and proves that **2b** is formed. Semiempirical calculations support the above conclusion. From Table 5, it is seen that **2b** is more stable than **2c** by 65 kJ mol^{-1}. Hence it seems that the N^+CH_2 hydrogen atoms are slightly more acidic than CH_2COO. α-Deprotonation of the second ring carbon was also observed when *N*-ethylpiperidine was treated with a super-base (*s*-BuLi–*t*-BuOK).[22]

A typical time-dependent UV spectrum showing the disappearance of **2b** is shown in Fig. 3. The ylides are not very stable compounds and slowly rearrange to more stable products. The ^{1}H NMR spectrum shows that cation **2a** on addition of P2-Et slowly undergoes elimination to give pyridine and ethyl acrylate (Fig. 4 Table 6), but the reaction does not go to completion, because these compounds remain in equilibrium. The elimination reaction of acrylates is reversible.[15] The formation of ethyl acrylate established that the elimination occurs via **2c**, which can be generated directly from **2a** and additionally *via* **2b** (Scheme 4). Thus P2-Et abstracts both α- and β-protons from **2a** but abstraction of the α-hydrogen atom is

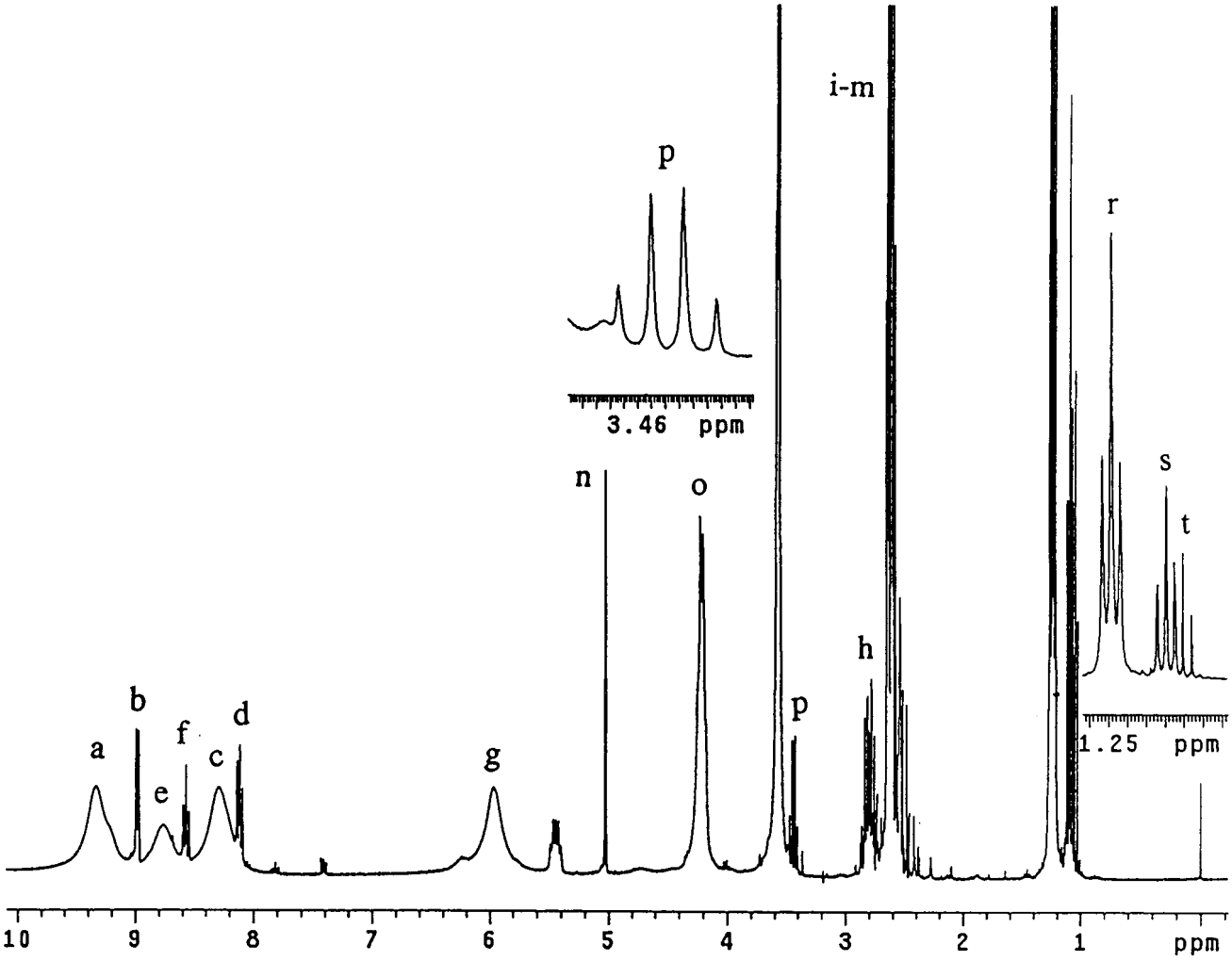


Figure 2. ^{1}H NMR spectrum of a mixture of **1a** and P2-Et in DMSO-d_6

the rate-determining step. The elimination step is much slower than the deprotonation reaction.

The time-dependent UV spectra of substituted 1-(2-cyanoethyl)pyridinium cations in aqueous alkaline solutions show that the reaction mixture is transparent above 300 nm.[15] The absorptions of the pyridinium cations are more intense than those of neutral pyridines but their wavelengths are comparable. The only exceptions are cations with amino and methoxy substituents, which show a more significant spectral change as a result of the resonance interactions of the substituents with the pyridine ring. These data show that *N*-(2-cyanoethyl)pyridinium cations in alkaline aqueous solution do not form ylides. Hence, the deprotonation mechanism of pyridine cations by strong bases in aprotic solvents is different from that in aqueous alkaline solution.

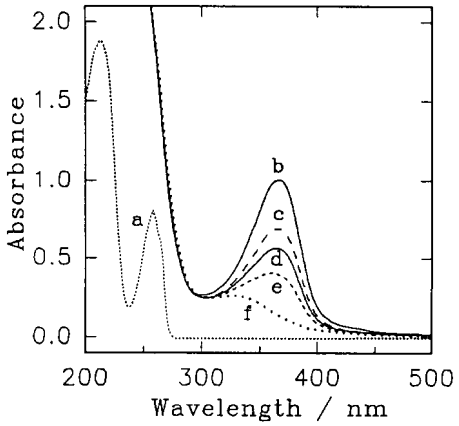


Figure 3. UV–visible spectra of (a) **2a** (5×10^{-5} M) and a mixture of **2a** (4×10^{-5} M) with P2-Et (1×10^{-2} M) in acetonitrile after (b) 0.5, (c) 6, (d) 12, (e) 18 and (f) 30 min

Table 5. Calculated heats of formation (ΔH_f) and dipole moments (μ)

Compound	ΔH_f (kJ mol^{-1})		μ (D)	
	PM3	SAM1	PM3	SAM1
1b	−94.98	−106.02	2.55	2.78
2b	−116.98	−111.54	2.10	2.30
2c	−44.56	−45.77	10.31	10.45

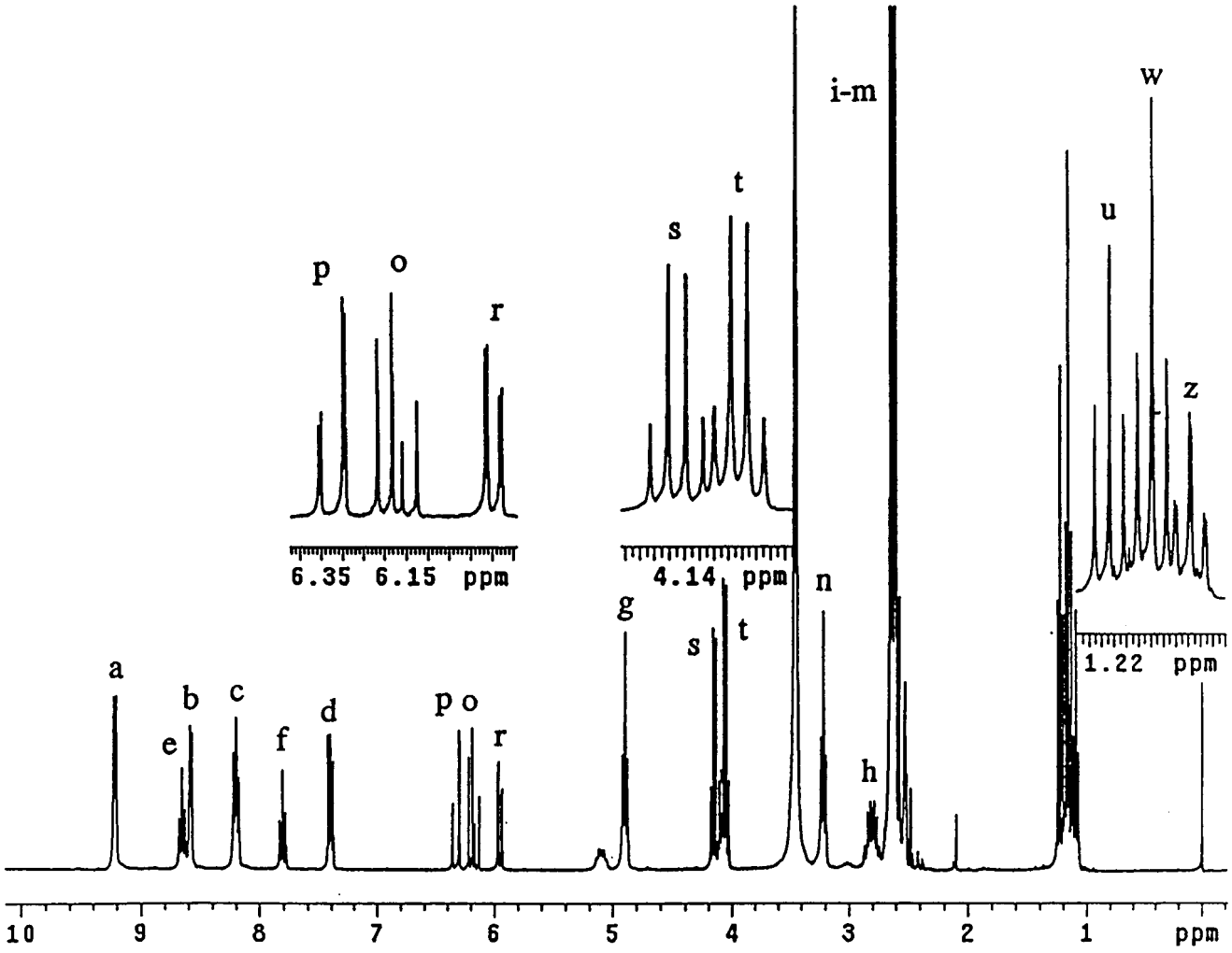
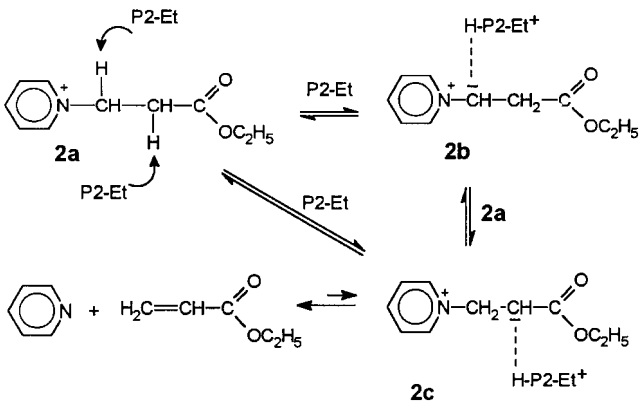


Figure 4. ^{1}H NMR spectrum of a mixture of **2a** with P2-Et in DMSO-d_6

CONCLUSIONS

The deprotonation of **la** with DBU, MTBD, TBD and P2-Et and **2a** with P2-Et in aprotic solvents has been investigated by kinetic measurements, UV and ^{1}H NMR spectroscopy and PM3 semiempirical calculations. The k_{obs} data fits Eqn (1) well. The UV spectra show that both compounds form ylides, which undergo decomposition. These decomposition reactions were followed by ^{1}H NMR spectroscopy. The *N*-methylpyridinium cation and ethanol were detected in the mixture containing **1a**, whereas pyridine and ethyl acrylate were detected in the mixture containing **2a**.

It is interesting that deprotonation of the 1-(2-cyanoethyl)pyridinium cation in aqueous alkaline solution does not proceed via ylides.[15] Thus deprotonation with strong bases in aprotic solvents differs from that in alkaline aqueous solution.

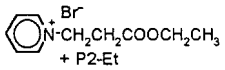
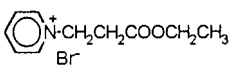
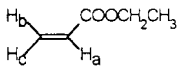


Scheme 4

EXPERIMENTAL

An equimolar mixture of pyridine and the appropiate ω-haloalkanecarboxylic ethyl ester was allowed to stand at room temperature until a solid was precipitated. This product was filtered off and washed with diethyl ether.

Table 6. ^{1}H NMR data for products resulting from the reaction between **2a** and P2-Et in DMSO-d_6[a]

Assignment		 + P2-Et		P2-Et		
H_α	a	9.18(d)	9.22(d)	—		—
	b	8.58(d)			8.59(d)	
H_β	c	8.19(t)	8.20(t)	—		—
	d	7.39(t)			7.41(t)	
H_γ	e	8.64(t)	8.66(t)	—		—
	f	7.80(t)			7.81(t)	
N-CH_2	g	4.88(t)	4.90(t)		—	—
	h	2.80(m)		2.89(m)		
N-CH_3	i	2.64(s)	—	2.61(s)	—	—
	j	2.63(s)		2.58(s)		
	k	2.61(s)		2.54(s)		
	l	2.60(s)		2.50(s)		
	m	2.52(s)				
CH_2COO	n	3.21(t)	3.19(t)	—	—	—
H_a	o	6.17(dd)	—	—	—	6.17(dd)
H_b	p	6.32(dd)	—	—	—	6.33(dd)
H_c	r	5.94(dd)	—	—	—	5.95(dd)
OCH_2	s	4.15(q)		—	—	4.15(q)
	t	4.06(q)	4.06(q)			
CH_3	u	1.23(t)			—	1.23(t)
	w	1.16(t)	1.15(t)			
	z	1.09(t)		0.95(t)		

[a] d = Doublet; m = multiplet; t = triplet; q = quartet.

The 1-(carbethoxyalkyl)pyridinium halides were very hygroscopic and could be hydrolysed to the corresponding 1-(carboxyalkyl)pyridinium halides by standing at room temperature for several weeks; 1-(carbethoxymethyl)pyridinium chlorides (**1a**), m.p. 62–65 °C (lit.,[23] m.p. 70 °C), 1-(2-carbethoxyethyl)pyridinium bromides (**2a**), m.p. 67–69 (lit.,[24] m.p. 70–72 °C).

The bases, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD), 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) and Schwesinger base, phosphazene base (P2-Et), were purchased from Fluka and were used as received.

Acetonitrile was purified by the method of O'Donnell *et al.*[25] with a final distillation from P_2O_5 (b.p. 81.5–82.0 °C).

The ^{1}H NMR spectra were recorded in DMSO-d_6 on a Varian Gemini 300VT spectrometer, operating at 300.07 MHz, using TMS as the internal standard. The spectra of the mixture of compounds **1a** or **2a** with P2-Et were measured immediately after preparation.

UV spectra were recorded in acetonitrile on a Hewlett-Packard diode-array spectrophotometer.

The kinetic runs for the deprotonation reaction were carried out using a stopped-flow spectrophotometer (Applied Photophysics) with the cell block thermostated to within $\pm$ 1 °C.

PM3[26] and SAM1[27] semiempirical calculations were performed using the AMPAC 5.0 program.[28] In all cases the PRECISE keyword was used and full geometry optimization was carried out without any symmetry constraints.

Acknowledgement

This work was supported by the Polish Committee for Scientific Research (KBN), grant 2P 303 06907.

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