The Effect of 4-Substituents on the Stability of Pyridinium Dicarbethoxymethylides

James E. Douglass, M. Wilson Tabor, and Julius E. Spradling, III

Department of Chemistry, Marshall University, Huntington, West Virginia 25701

The effect of 4-substituents on the stability of pyridinium dicarbethoxymethylides, as determined by pK_a measurements, is found to correlate well with their effect on the stability of similarly substituted pyridine 1-oxides. Displacements in chemical shift in the ylides, particularly of the α-protons, are also found to correlate well with substituent effects. Intramolecular charge-transfer transitions in the electronic spectra, characteristic of pyridinium ylides, are reported.

While the electronic properties of pyridine 1-oxides have been studied in very considerable detail (1), similar investigations of the closely related pyridinium ylides have been meager despite their demonstrated synthetic usefulness (2,3). Following the lead of Ragsdale and coworkers (4) who have found linear free energy relationships among the chemical and physical properties of 4-substituted pyridine 1-oxides, we chose to study a series of similarly substituted pyridinium methylides (see Table I).

Dicarbethoxymethylides (2) were selected for several reasons: (1) ready synthesis starting with the 4-substituted pyridine and diethyl bromomalonate, (2) sufficient stability to be handled and stored in air, and (3) a conveniently measurable range of pK_a values.
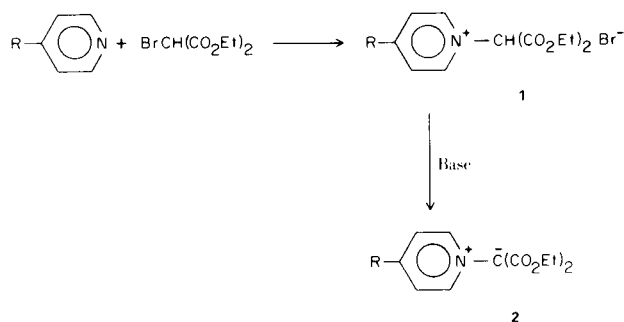

Isolation of the intermediate pyridinium salts 1 is not feasible because their relatively great acidity (vide infra) insures substantial deprotonation by unreacted amine to give the corresponding ylides 2. For example, when R = H the equilibrium constant for this acid-base reaction is about 1.2. Hence it is desirable to use an excess of the
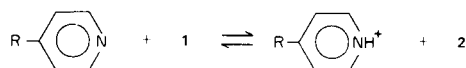

pyridine and then treat the initial reaction mixture with sodium carbonate solution to complete the conversion of 1 to 2.

During the course of this investigation Phillips and Ratts (5) reported the results of a similar study of 4-substituted pyridinium phenacylides (3). Our results complement and extend theirs.
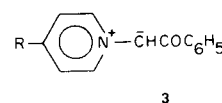
Linear Free Energy Relationships.

Resonance theory does not permit an unambiguous prediction of the type of 4-substituent which should stabilize a pyridinium ylide. An electron-donating group (e.g., methoxy) can delocalize the positive charge, whereas an electron-withdrawing group (e.g., acetyl) can delocalize the negative charge, as shown by the following canonical structures of 2b and 2e.
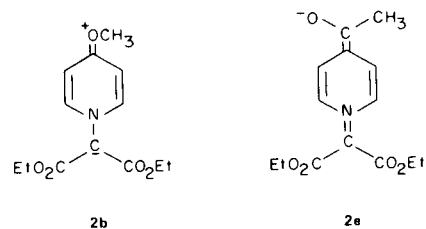
The effect of 4-substituents on stability can be ascertained, however, by measuring the pK_a's of the ylides, the values of which are shown in Table I. Qualitatively, it is clear from these results that electron-withdrawing substituents are stabilizing, whereas electron-donating groups are destabilizing with respect to hydrogen. This trend is precisely the same as that reported for 4-substituted

TABLE I

4-Substituted Pyridinium Dicarbethoxymethylides

Compound Number	R	Color	M.p., °C	pK_a	Molecular Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
2a	N(CH₃)₂	white	165-166	6.65	$C_{14}H_{20}N_2O_4$	59.99	7.19	9.99	60.13	7.15	10.11
2b	OCH₃	yellow	160-162	5.70	$C_{13}H_{17}NO_5$	58.41	6.41	5.24	58.55	6.52	5.08
2c	CH₃	yellow	206-207	5.34	$C_{13}H_{17}NO_4$	62.13	6.82	5.58	61.96	6.95	5.70
2d	H	yellow	172-173	5.12	$C_{12}H_{15}NO_4$	60.75	6.37	5.90	60.27	6.37	5.79
2e	COCH₃	red-orange	196-198	4.62	$C_{14}H_{17}NO_5$	60.20	6.14	5.02	59.97	6.06	4.95
2f	CO₂CH₃	red	174-175	4.56	$C_{14}H_{17}NO_6$	56.94	5.80	4.74	56.69	5.84	4.69
2g	CN	red	~240 dec.	4.15	$C_{13}H_{14}N_2O_4$	59.53	5.38	10.68	59.42	5.14	10.55

pyridine 1-oxides (4) and pyridinium phenacylides (5).

The quantitative relationships are revealed in the Hammett plots of $(pK_O\text{-}pK)_{ylide}$ vs. $(pK_O\text{-}pK)_{PyO}$ shown in Figure 1 (6). The data both from our ylides and those of Phillips and Ratts (5) are plotted. The excellent correlations observed demonstrate that the electronic influence of R in the ylides is linearly related to its effect in the pyridine 1-oxides. However, the markedly lower ρ value for the dicarbethoxymethyl system compared to the phenacyl system (0.47 and 1.37, respectively) strongly indicates that the electronic influence of R is much less effectively transmitted to the reaction site in the former.

This difference may be due in large measure to differences in steric interactions about the methylide carbon atoms which carry substituents of differing size in these

two classes of ylides. Maximum electronic interaction of a 4-substituent requires that the exocyclic methylide grouping be coplanar with the pyridine ring, a condition which in ylides 2 would generate two quite unfavorable steric interactions involving the two carbethoxy groups and 2-H and 6-H on the ring. Only one such nonbonded interaction would exist in the phenacylides. Thus, the dicarbethoxymethylides should depart significantly from planarity, a condition which could be achieved in one of two ways: (1) rotation about the nitrogen-methylide carbon bond, which would place one carbethoxy group above and one below the plane formed by the ring and methylide carbon (4); or (2) orbital hybridization on the methylide carbon favoring tetrahedral rather than trigonal geometry, which would place both carbethoxy groups below the plane (5).
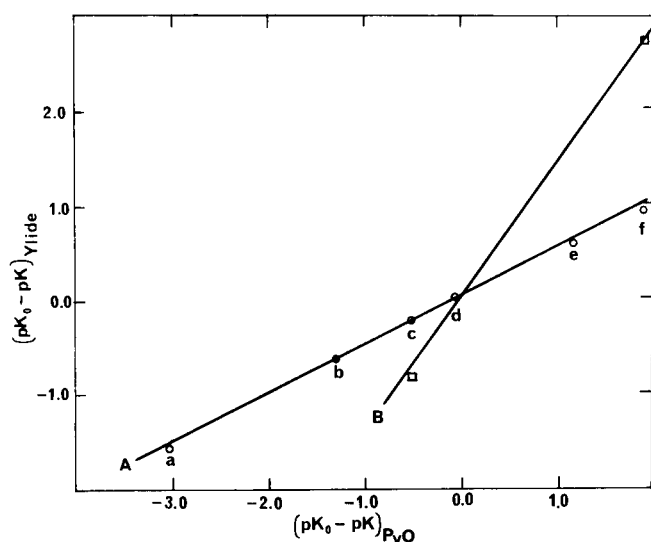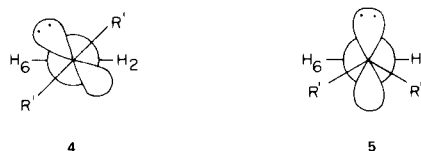

It seems relevant to the latter argument to note that in pyridinium dicyanomethylide, the only pyridinium ylide for which a complete x-ray structure determination has been reported (7), the two cyano groups project slightly (ca. 3°) below the plane formed by the ring and the methylide carbon atom.

Nuclear Magnetic Resonance Spectra.

At 100 MHz the aromatic protons of the 4-substituted pyridines, pyridinium salts (1), and ylides (2) show clean $AA'XX'$ patterns (J_{23} = 6-8 Hz, J_{25} = 0.5-1.5 Hz). Several trends in the chemical shifts of these protons are readily apparent (see Table II). First of all, in going from the 4-substituted pyridine to the corresponding 1-dicarbethoxymethylpyridinium salt (1), both 2-H and 3-H are shifted downfield in the expected manner (8).

Figure 1. Plots of $(pK_O\text{-}pK)$ of ylides 2a-f (line A, this work) and ylides 3 (line B, ref. 5) versus $(pK_O\text{-}pK)$ of the corresponding 4-substituted pyridine 1-oxides (ref. 4).

TABLE II

NMR Data

| R | 2-H, δ (ppm) | | | 3-H, δ (ppm) | | |
	Pyridine (a)	Salt (b)	Ylide (a)	Pyridine	Salt	Ylide
N(CH₃)₂	8.18	- - -	7.93	6.44	- - -	6.65
OCH₃	8.44	- - -	8.34	6.77	- - -	7.15
CH₃	8.43	9.03	8.47	7.05	8.34	7.45
H	8.60	9.18	8.63	7.00	8.31	7.77
COCH₃	8.77	- - -	8.83	7.70	- - -	8.06
CO₂CH₃	8.76	- - -	8.85	7.80	- - -	8.17
CN	8.87	- - -	8.98	7.62	- - -	8.38

(a) In deuteriochloroform, TMS as internal standard. (b) Hexafluorophosphates, in DMSO-d₆, TSS as internal standard.

However, upon conversion to the ylide (1), both 2-H and 3-H shift upfield, with the former moving back to very near its position in the starting pyridine. This is in agreement with the previously reported (3e) nmr data on ylide 2d (R = H), and supports the proposal of Henrick and coworkers (3e) that there is considerable delocalization of the negative charge into the ring which thereby restores electron density at C-2 to very near its original value. Phillips and Ratts (5), on the other hand, find that in the pyridinium phenacylides, 2-H is shifted downfield with respect to its position in the corresponding salt. They explain this behaviour in terms of the deshielding effect expected if the oxygen atom of the benzoyl group were constrained to a position close to 2-H (9), as would be the case if the molecule were very nearly planar. To the extent that this is a valid argument, it supports the contention discussed above that the pyridinium dicarb-

ethoxymethylides must depart substantially from planarity.

Lastly, 4-substituents in the ylides qualitatively have the expected effect upon the chemical shifts of both 2-H and 3-H; i.e., electron-donating groups shield them, whereas electron-withdrawing groups deshield them with respect to the parent ylide. Although 3-H, being adjacent to the substituent, shows a greater range of displacements in chemical shifts, 2-H shows a somewhat more uniform trend in its displacements. This is clearly revealed by the plot of displacement in chemical shift (Δδ) vs. $(pK_o\text{-}pK)_{ylide}$ shown in Figure 2, and indicates that the 4-substituent is exerting a linear effect upon electron density at 2-C (10).

Intramolecular Charge-Transfer Bands.

The most obvious property of the ylides is the marked dependence of their color upon the 4-substituent (see Table I). Those with electron-donating groups are white to pale yellow, while those with electron-withdrawing groups are reddish-orange to deep red in the solid phase. The color of the ylide in solution, however, is strikingly dependent upon the nature of the solvent. For example, the 4-carbomethoxy ylide (2f), which is red solid, is yellow in water, red in chloroform, and purple in benzene. This pronounced bathochromic shift in the longest wavelength band in the uv-visible spectrum with decreasing solvent polarity is typical for pyridinium ylides (3e,11), and is a phenomenon characteristic of intramolecular charge-transfer transitions (12). See Table III for the charge-transfer bands of the ylides in water and chloroform.

It should also be noted that the 1-dicarbethoxymethylpyridinium bromides also show a solvent-sensitive band in their electronic absorption spectra, indicative of intermolecular charge-transfer transitions.
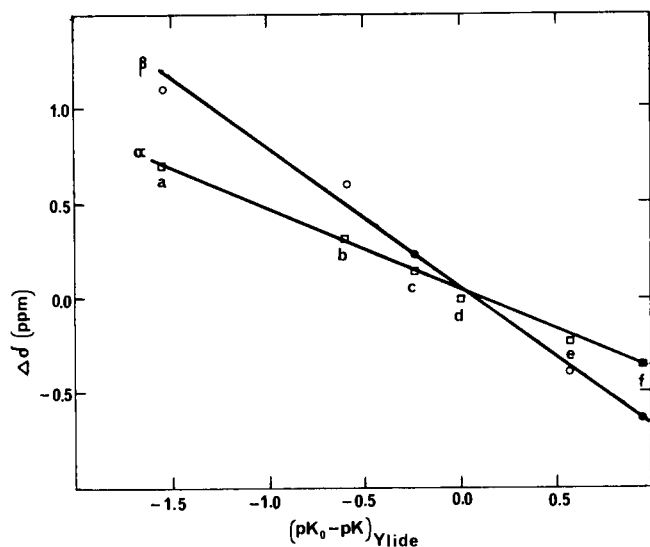

Figure 2. Plots of displacements in chemical shifts (Δδ) of the α- and β-protons versus $(pK_o\text{-}pK)$ of ylides 2a-f.

TABLE III

Intramolecular Charge-Transfer Bands

R	Solvent	λ max, nm	log ε
NMe$_2$	H$_2$O	a	
	CHCl$_3$	363	3.44
OMe	H$_2$O	332	3.02
	CHCl$_3$	385	3.20
Me	H$_2$O	360	3.10
	CHCl$_3$	425	3.38
H	H$_2$O	366	3.01
	CHCl$_3$	435	3.49
COMe	H$_2$O	402	3.14
	CHCl$_3$	522	3.33
CO$_2$Me	H$_2$O	435	3.27
	CHCl$_3$	515	3.79
CN	H$_2$O	430	3.27
	CHCl$_3$	514	3.55

EXPERIMENTAL (13)

Pyridinium 1-Dicarbethoxymethylides (2).

A mixture of 40 mmoles of 4-substituted pyridine and 20 mmoles of diethyl bromomalonate was allowed to stand at room temperature under dry nitrogen for 24 hours. (In the case of 4-cyanopyridine it was necessary to warm the mixture on a steam cone for 8 hours). Water (25 ml.) was added and the resulting mixture was heated to 70° and stirred for 10 minutes. The aqueous layer was decanted from the small amount of dark, viscous residue, allowed to cool and then washed with a 25-ml. portion of ether. The washed solution was made alkaline by the addition of 20 ml. of 10% aqueous sodium carbonate and extracted with three 25-ml. portions of chloroform. After drying the combined extracts over anhydrous potassium carbonate, the volume was reduced to about 10 ml. on a rotary evaporator. The resulting solution was added slowly to 150 ml. of rapidly stirred hexane at room temperature. The ylide which precipitated was collected on a filter, washed with a small amount of hexane and dried. One recrystallization from acetone was usually sufficient to afford material of analytical purity. Yields were in the range of 35-60%. See Table 1 for melting points and elemental analyses.

Hexafluorophosphate salts (1) were prepared by adding an aqueous solution of the ylide to an equimolar amount of 65% hexafluorophosphoric acid diluted with an equal volume of ethanol. The precipitated salt was filtered off and recrystallized from hot water. None of the salts were sufficiently soluble in deuterium oxide to obtain satisfactory nmr spectra, and only two (1c and 1d) were sufficiently soluble in DMSO to give useful spectra.

pK_a Determinations.

The procedure used to determine pK_a's was essentially the same as that described by Shechter and coworkers (14). About one millimole of ylide dissolved in 50 ml. of water was titrated potentiometrically with standardized hydrochloric acid (0.1N). Endpoints were determined by the second derivative method.

The pH was plotted vs. ml. of added titrant, and the pK_a was calculated at one-third, one-half, and two-thirds neutralization using the following equation.

$$pK_a = pH + \log [HA]/[A^-]$$

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(10) There are several assumptions implicit in this interpretation, the most important of which are substituent-independence of the ring current effect and negligible long-range substituent field effects at 2-C. See ref. 8c and J. M. Haigh and D. A. Thornton [Tetrahedron Letters, 2043 (1970)] for discussion of these problems.

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