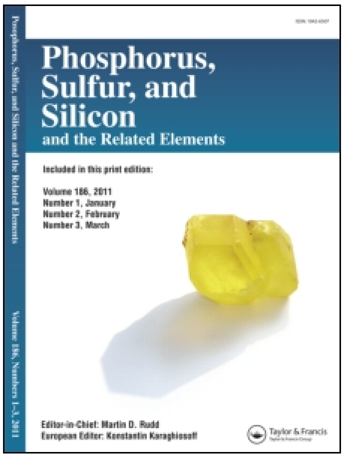

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STUDIES ON THE REACTIVITY PATTERNS OF HETEROCYCLICS IN AQUEOUS DMSO-INTERACTION BETWEEN POSITIVE END OF SULFOXIDE DIPOLE AND LONE PAIR ON RING NITROGEN IN PYRIDINE DERIVATIVES

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STUDIES ON THE REACTIVITY PATTERNS OF HETEROCYCLICS IN AQUEOUS DMSO–INTERACTION BETWEEN POSITIVE END OF SULFOXIDE DIPOLE AND LONE PAIR ON RING NITROGEN IN PYRIDINE DERIVATIVES

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ABSTRACT

The signals for the α, β, and γ protons of pyridine exhibit a downfield shift in DMSO-d_6, compared to CCl_4 as solvent, the order being $\gamma > \beta > \alpha$. This is attributed to an interaction between the positive end of the DMSO dipole and the lone pair of electrons on the ring nitrogen. This effect is also reflected in the faster rate of alkaline hydrolysis of ethyl isonicotinate over ethyl nicotinate and ethyl picolinate in aqueous DMSO relative to aqueous ethanol. Similar solvent effects are also observed in the pmr spectrum of pyrazine.

In our recent communication[1] in explaining the results of Jang and coworkers on the nmr spectra of 2′-deoxyadenosine in aqueous DMSO,[2] we had postulated an interaction between the positive end of the sulfoxide dipole in DMSO and the lone pair of electrons on the ring nitrogen atoms. In order to test out our hypothesis, we have now studied the nmr spectra of pyridine in three solvents (CCl_4, $CDCl_3$ and DMSO-d_6) as well the kinetics of the alkaline hydrolysis of the three pyridine carboxylates in binary solvent mixtures of ethanol-water and DMSO-water. The results are analyzed in terms of the possible interaction between the positive end of the DMSO dipole and the lone pair of electrons on the ring nitrogen.

TABLE I

PMR Data for Pyridine

Proton	δ values in ppm			$\Delta\delta^b$	$\Delta\delta^c$
	$^aCCl_4$	$CDCl_3$	DMSO-d_6		
α	8.50	8.60	8.62	0.12	0.25
β	7.06	7.24	7.39	0.33	1.07
γ	7.46	7.64	7.88	0.42	1.22

[a] Data in CCl_4 from W. McFarlene, "Elucidation of organic structures by physical and chemical methods—Part I" Ed. by K. W. Bentley and G. W. Kirby, p. 269.

[b] $\Delta\delta = \delta_{CCl_4} - \delta_{DMSO\text{-}d_6}$.

[c] Shifts due to protonation—data for the downfield shifts for protonated pyridine are from reference 3 and reference 5.

Table I presents the nmr data of pyridine in the three solvents. It is known that the protonation of the ring nitrogen in pyridines leads to certain interesting features in the nmr spectrum: i) the β and γ proton signals are displaced downfield by 1.07 and 1.22 ppm respectively, whereas the α-proton signal is shifted by only 0.25 ppm; 3,5-leutidine and γ-picoline cations also show a similar phenomenon,[3] ii) On protonating pyridine, the N^{15} signal is displaced by 123 ± 11 ppm to high field.[4]

There is convincing evidence that the lone pair of an sp^2-hybridized nitrogen atom is associated with appreciable anisotropy. This is predicted theoretically as being associated with the low lying excited state involved in the $n \rightarrow \pi^*$ transitions of such systems. Gil and Murrel[5] calculated the anisotropy of the nitrogen atom in pyridine and found that this value accounts

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[1] G. Venkoba Rao, M. Balakrishnan and N. Venkatasubramanian, *Polymer*, **14**, 332 (1973).

[2] C. G. Jang, P. Bartl and T. Williams, *Polymer*, **13**, 520 (1972).

[3] I. C. Smith and W. G. Schneider, *Can. J. Chem.*, **39**, 1158 (1961).

[4] J. D. Baldeschwielder and E. W. Randall, *Proc. Chem. Soc.*, 303 (1961).

[5] U. M. S. Gil and J. N. Murrel, *Trans. Farad. Soc.*, **60**, 248 (1964).

TABLE II

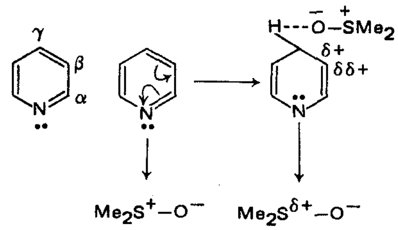
Rate Constants for the Alkaline Hydrolysis of Pyridine Carboxylates

Temp: 30°C; $10^1 k$ (liter mol^{-1} sec^{-1})

	Solvent (% v/v)					
	50% DMSO	60% DMSO	70% DMSO	50% EtOH	60% EtOH	70% EtOH
Ethyl picolinate	11.4	15.9	22.6	1.79	1.42	1.36
Ethyl nicotinate	9.36	14.3	20.7	1.19	0.854	0.799
Ethyl isonicotinate	39.0	88.5	156	4.74	4.48	4.06

quite well for the shift in the N^{15} resonance of pyridine on protonation. This anisotropy gives rise to deshielding of protons in the plane of the ring, an effect which is, of course, greatest at the α-position. The anisotropy is substantially reduced by the protonation of the ring nitrogen atom with the result that the chemical shift of the α-proton is only slightly affected by protonation, whereas the β- and γ-protons are considerably shifted to lower fields. At the α-position the deshielding effect of the positive charge is largely cancelled by the reduction in the anisotropy of the nitrogen atom. Similar effects have been predicted for sp^2 nitrogen atoms in other systems such as Schiff's bases, oximes, etc.[6]

On the above basis, one should expect to observe a similar effect if there is an interaction between the positive end of the sulfoxide dipole in DMSO and the ring nitrogen atom. This is exactly what is observed in our systems. The magnitude of the interaction being less, smaller shifts are naturally observed. We envisage the interaction between the ring nitrogen and the positive end of the sulfoxide dipole in the following fashion.



It is evident that structure 2 will be more stable because of the *p*-quininoid structure. This solvent-solute interaction conceived will thus cause a greater development of the positive charge on the γ-carbon atom. This will lead to the proton attached to the γ-carbon atom (and to a smaller extent the proton on the β-carbon) resonating at a lower field. As Gil and Murrel have shown for protonated pyridine, the deshielding effect of the positive charge at the α-position is largely cancelled by the reduction in the anisotropy of nitrogen on protonation or coordination. These effects must be felt to a smaller extent in $CDCl_3$ and hence the smaller shifts.

In Table II are presented the rates of alkaline hydrolysis of pyridine 2-, 3- and 4-carboxylates in aqueous ethanol and aqueous DMSO. The increased hydrolytic rates in aqueous DMSO when compared with aqueous ethanol are in accord with the foregoing postulates.

If the development of positive charge on the α-, β- and γ-carbon atoms is more in aqueous DMSO, then one would expect that the transition states for the hydrolysis of the corresponding esters would also become "tighter" and consequently more stabilized by the dipolar aprotic solvent DMSO. Parker and Ko[7] have come to the conclusion, from their studies of dipolar aprotic solvent effects on S_N2, E_2H and E_2hal. reactions, that electron attracting groups attached to the reaction centres of the above mentioned reactions increase the tightness of the transition states, thus

TABLE III

$^{a}k_s$ Values for Ethyl *p*-Substituted Benzoates Saponification at 25°C

Compound	k_s
Ethyl *p*-nitrobenzoate	580
Ethyl benzoate	400
Ethyl *p*-chlorobenzoate	439
Ethyl *p*-methoxybenzoate	290

$k_s = k_{DMSO}/k_{EtOH}$

[a] From reference 8 in aqueous DMSO/EtOH with mol fraction of DMSO/EtOH = 0.69.

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[6] L. M. Jackmann and S. Sternhill, 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry' Pergamon Press, Oxford (1969), p. 208.

[7] A. J. Parker and E. C. F. Ko, *J. Am. Chem. Soc.*, **90**, 6447 (1968).

TABLE IV

k_s Values for the Saponification of Pyridine Carboxylates at 30°C[a]

Ester	Composition of solvent[b] 50% Solvent	 60% Solvent	 70% Solvent
Ethyl picolinate	6.37	11.2	16
Ethyl nicotinate	7.80	16.7	26
Ethyl isonicotinate	8.22	20.0	38
Ethyl benzoate	—	—	44

[a] Present work.

[b] Percentage (v/v) of DMSO/EtOH in the aqueous solvent mixture.

making them solvated to a greater extent by the dipolar aprotic solvent. The same effect is found in ester saponifications, and this would be clear from the data for the hydrolysis of substituted ethyl benzoates in aqueous DMSO and aqueous ethanol.[8] The k_s value ($= k_{DMSO}/k_{EtOH}$) is found to be much higher for *p*-nitrobenzoate than for *p*-methoxy benzoate (Table III). On the basis of this one would expect a larger k_s value for ethyl isonicotinate and ethyl nicotinate compared to ethyl picolinate and this is what is observed (Table IV).

A consideration of the comparative rate data (k_s values presented in Table IV) in the light of the following equation originally proposed by Parker[9] for S_N2 reactions and successfully applied by us for alkaline ester hydrolyses[10] is consistent with the above proposal.

$$\log k^D/k^E = \log {}^E\gamma^D_{OH^-} + \log {}^E\gamma^D_{ester} - \log {}^E\gamma^D_{ts}$$

The 'γ' terms in this equation represent the solvent activity coefficients for the reactants, OH^- ion and the ester and the transition state(ts), E denoting ethanol and D denoting DMSO. The proposed sulfoxide dipole–ring nitrogen interaction would amount to greater solvation of the ester molecule by DMSO, thereby tending to make the corresponding 'γ' term *less positive* with a concurrent decrease in the k_{DMSO}/k_{EtOH} value, compared to ethyl benzoate where the above situation is absent—hence the considerable lowering of k_s value for picolinate relative to the benzoate ester. The developing positive charges at β and γ positions for ethyl nicotinate and isonicotinate respectively increase the "tightness" of the respective transition states for the hydrolysis leading to *more negative* values for γ_{ts} term and higher k_s values. Thus the two mutually opposing influences tend to keep the k_s values for these two esters to approach that of ethyl benzoate.

TABLE V

Solvent Effects on the PMR Spectra of Pyrazine[a]

Solvent	δ ppm
CCl_4	8.48
$CDCl_3$	8.50
DMSO-d_6	8.68
CF_3COOH	9.36[b]

[a] Present work.

[b] Such downfield shifts on protonating pyrazine have been reported earlier (R. J. Pugmine and D. M. Grant, *J. Am. Chem. Soc.*, **90**, 697 (1968)).

We wish to add that the nmr signals for pyrazine (Table V) follow a parallel trend, *i.e.*, to the downfield in DMSO-d_6 and on protonation (with CF_3COOH) substantiating a case for such sulfoxide dipole-ring nitrogen interaction.

The nmr spectra were measured through the courtesy of Dr. A. J. Parker at the Research School of Chemistry, Australian National University, Canberra and of Prof. M. V. Bhatt at the Indian Institute of Science, Bangalore using a Varian 100 mHz nmr Spectrometer.

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8. M. Hojo, M. Utaka and Z. Yoshida, *Tetrahedron Lett.* 25 (1966).
9. A. J. Parker, *Chem. Rev.*, **69**, 1 (1969).
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