

A study of substituent effects on the NH bond in alkyl and aryl 4,6-disubstituted-3-cyano-2-pyridones*

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Abstract: Substituent effects on the IR stretching frequencies and ¹H-NMR chemical shifts of the pyridone NH group in 4- and 6-disubstituted alkyl and aryl 3-cyano-2-pyridones were investigated. The bands most sensitive to substituent effects from the broad and multiple IR NH band for each compound were selected by a computer calculation. The selected values of the IR frequencies and the determined ¹H-NMR chemical shifts were subjected to LFER analysis, by correlations with the Hamett $\sigma_{m/p}$ and Swain–Lupton *F* and *R* substituent constants.

Keywords: substituted 2-pyridones, LFER analysis, NH bond, IR and ¹H-NMR spectra.

INTRODUCTION

In a recent paper,¹ an investigation of the spectral characteristics of the title compounds was reported. The effects of substituents in the 4 and 6 positions of the 2-pyridone nucleus on CN, CO, ring and 5H functions were estimated there, by applying the LFER principles. At that time, it was not possible to report on the effect of substituents on the NH bond, due to the well known controversy of the broad multiple NH band in the IR spectra, which is otherwise the most interesting functional group in 2-pyridones. In the present paper, for the same three series of compounds from the previous work, of the general formulae shown in Scheme 1, the data on the NH IR stretching frequencies and the ¹H-NMR chemical shifts were subjected to correlation analysis using the LFER principles, with the intention of gaining information concerning the transmission of substituent effects to the NH bond. It was believed that this is important because of the known potential biological activity of substituted pyridones.¹ It is reasonable to expect, due to the presence of the CONH group in the pyridone molecule and the similarity

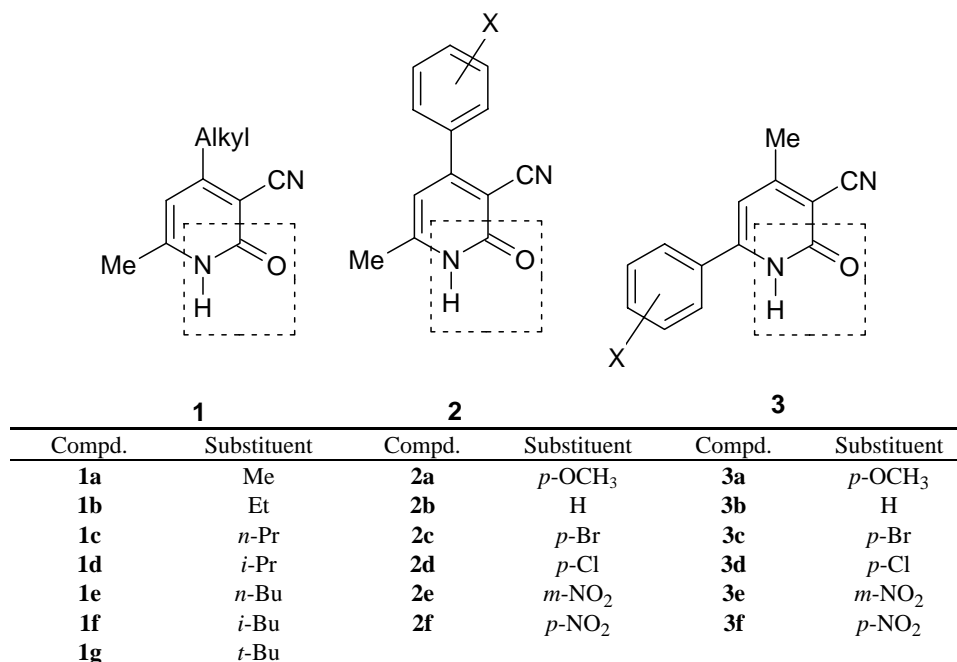
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of this group to the peptide bond in proteins, that the interactions of 2-pyridone derivatives with natural substrates would occur *via* the hydrogen bond formation between the two complementary functions.



Scheme 1. General structures of the investigated 4,6-disubstituted-3-cyano-2-pyridones.

In the first investigation of the IR spectra of the NH bond in 2-pyridones,² the main peak in the solid state was assigned at 3100 cm⁻¹ and at 2850 cm⁻¹ in solution. In both forms, broad multiple bands were observed with well resolved subsidiary peaks. Later, it was claimed³ that 2-pyridones exist as hydrogen bonded spiral dimers both in the solid state and in concentrated solutions, with the NH peaks very broad and strong with many maxima in the region 3200–2800 cm⁻¹. It was also observed that some free ν_{NH} frequencies were found at *ca.* 3400 cm⁻¹ in dilute CCl₄ solutions and in the gas phase at 3448 cm⁻¹.⁴ Recently, the IR spectra of the 2-pyridone NH bond were used to study 2-pyridone/2-hydroxypyridine tautomerism in the context of water clusters in supersonic jets,^{4,5} and as analogues for biological systems,^{6,7} or for comparison in a theoretical study of the same phenomenon.⁸ In all these studies, broad multiple NH bands were observed, and the main peak was estimated as above. However, it should be pointed out that all these studies refer to unsubstituted 2-pyridone.

EXPERIMENTAL

All substances, the spectral characteristics of which are presented in the present paper and were used for correlations with the LFER parameters, were synthesized by literature methods or by ana-

logy to those, sometimes by modified procedures. Some of these were new compounds, fully characterized by IR, NMR, MS and UV spectroscopy, and were reported in previous communications.⁹⁻¹¹

The LFER equations and substituent constants employed for the calculations were taken from the standard texts on the subject.^{12,13}

A computer calculation based on Fortran 77 was devised and used for the selection of IR frequencies of investigated alkyl and aryl 2-pyridones with the highest sensitivity to substituent effects. Experimental values of frequencies with well-defined peaks from the broad multiple NH band were used. In a stepwise elimination procedure, in the predetermined range of regression coefficients 0.970–0.999, corresponding alkyl and aryl IR frequencies for each investigated compound were obtained. These are given in Tables I and II and were subjected to regression analysis, and the corresponding statistical parameters are presented in Eqs. (1), (2), (4), (5) and (8).

TABLE I. IR stretching frequencies and ¹H-NMR chemical shifts for the NH bond in 4-alkyl-6-methyl-3-cyano-2-pyridones

Compd.	Substituent	ν_{NH} (KBr) / cm^{-1}	δ_{NH} (DMSO- <i>d</i> ₆) / ppm
1a	Me	2996	12.24
1b	Et	2982	12.40
1c	<i>n</i> -Pr	2957	
1d	<i>i</i> -Pr	2975	12.26
1e	<i>n</i> -Bu	2986	
1f	<i>i</i> -Bu	2963	
1g	<i>t</i> -Bu	3019	11.53

The instruments used in the investigation were as follows: the IR spectra were recorded on Perkin–Elmer FTIR 1725x and Bomem MB 100 FTIR spectrophotometer. ¹H-NMR spectra were determined in DMSO-*d*₆ on a Varian–Gemini 200 MHz spectrometer using TMS as the internal standard.

TABLE II. IR stretching frequencies and ¹H-NMR chemical shifts for the NH bond in 4(6)-aryl-6(4)-methyl-3-cyano-2-pyridones (KBr)

Compd.	Substituent	ν_{NH} (KBr) / cm^{-1}	δ_{NH} (DMSO- <i>d</i> ₆) / ppm
4-Aryl substitution			
2a	<i>p</i> -OCH ₃	3134	
2b	H	3054	12.61
2c	<i>p</i> -Br	3020	
2d	<i>p</i> -Cl	3013	
2e	<i>m</i> -NO ₂	2899	
2f	<i>p</i> -NO ₂	2897	12.75
6-Aryl substitution			
3a	<i>p</i> -OCH ₃	3131	12.48
3b	H	3066	12.55
3c	<i>p</i> -Br	3018	12.60
3d	<i>p</i> -Cl	3019	12.62
3e	<i>m</i> -NO ₂	2928	12.80
3f	<i>p</i> -NO ₂	2898	

RESULTS AND DISCUSSION

No attempt to resolve the broad multiple NH band in the IR spectra of substituted 2-pyridone, not even for 2-pyridone itself, were found in the literature. In all literature references, the IR NH absorption is described as a broad band of peaks of approximately the same intensity, but usually one is singled out, being called the main peak at 3100 cm^{-1} ,² the bonded NH frequency (the middle-band or peak absorption) at 2700 cm^{-1} ,³ or a bound NH stretch as a sharp band at 3140 cm^{-1} .⁷ It has been stated that 2-pyridone in the solid state, in KBr and Nujol mull, exists exclusively in the oxo-form.^{2,3} In a fairly recent Japanese database, absorption of 2-pyridone in the IR region $3119\text{--}2880\text{ cm}^{-1}$ was also assigned to its oxo-form.

In the present investigation, the IR spectra of 4,6-disubstituted-3-cyano-2-pyridones were recorded in the form of KBr pellets on two instruments with very good resolution and the corresponding spectra from both were practically the same. The spectra of the three series of 4,6-disubstituted-3-cyano-2-pyridone shown in Scheme 1 have a broad band in the IR region $3200\text{--}2300\text{ cm}^{-1}$, but the absorption bands which vary with the substituent, and presumably indicate substituent effects on the NH bond, were in a more narrow region $3150\text{--}2750\text{ cm}^{-1}$. The absorption frequencies outside of this region are few and more or less constant, therefore not sensitive to substituent effects. Peaks in the region $3100\text{--}3000\text{ cm}^{-1}$ did not show appreciable substituent effects, as the corresponding correlation coefficients with the Hammett $\sigma_{p/m}$ constant were extremely low, which was also true for the region $2850\text{--}2750\text{ cm}^{-1}$. Therefore, it was decided to select by a computer calculation, absorption bands in the mid-region $3140\text{--}2880\text{ cm}^{-1}$, which gave the best fit to the Hammett equation with $\sigma_{p/m}$ constants as a standard test for the existence of an LFER relationship. This method was applied to both alkyl and aryl substituted 3-cyano-2-pyridones. The selected frequencies are presented in the Tables I and II and were used in the calculations presented in the following section. These values expectedly give the best correlations with both 2 and 3 parameter equations.

There was not sufficient data available for correlations of the $^1\text{H-NMR}$ chemical shifts, due to the insolubility of the investigated compounds in CDCl_3 and $\text{DMSO-}d_6$. Also, some of the compounds did not show visible peaks in the range of the NH bond, probably due to the inadequate sensitivity of the employed instruments.

4-Alkyl-6-methyl-3-cyano-2-pyridones (compounds 1a–f)

The IR stretching frequencies of the alkyl substituted series (Table I) selected in the above described manner were correlated with Hammett $\sigma_{m/p}$ constants and the result is presented in Eq. (1).

$$\nu_{\text{NH}} = (-772.61 \pm 71.02)\sigma_p + (2863.37 \pm 12.03) \quad (1)$$

$$R = 0.976, s = 4.97, n = 7, F = 100.6$$

Except for the relatively high standard error, the correlation is fairly good, considering the weak electronic effects of the alkyl groups. Similar result was obtained by use of the Swain–Lupton parameters, Eq. (2):

$$\nu_{\text{NH}} = (-884.87.18 \pm 102.70)F + (-742.18 \pm 72.18)R + (2868.45 \pm 11.34) \quad (2)$$

$$R = 0.984, s = 4.47, n = 7, F = 63.4$$

Only four compounds from the alkyl series were sufficiently soluble in DMSO- d_6 for the $^1\text{H-NMR}$ spectra to be recorded but had sufficiently different and well-defined chemical shifts for the NH group. The corresponding correlation is presented in Eq. (3):

$$\delta_{\text{NH}} = (16.07 \pm 3.47)\sigma_{\text{p}} + (14.81 \pm 0.58) \quad (3)$$

$$R = 0.956, s = 0.14, n = 4, F = 21.4$$

It is interesting to note that neither of the above correlations required correction with the steric parameters. Actually, the inclusion of these parameters gave inferior results, which is opposed to that observed in a previous study.¹

The obtained high standard deviations in the correlations of IR spectra could perhaps be explained by interference with the IR absorption in the same region of methyl and methylene groups and also the aromatic C–H stretching absorption from the 5H C–H bond. These disturbances are probably not very strong but are not constant and, except for the aromatic 5H, could cause dispersion of the data points.

4(6)-Substituted aryl-6(4) methyl-3-cyano-2-pyridones (compounds 2a-f and 3a-f)

In the previous investigation¹ on the correlation analysis on the same series of compounds as here, the effects from aryl substituents in positions 4 and 6 of the 3-cyano-2-pyridones on the CN, CO, ring and 5H groups was studied separately. In treating the broad multiple peak IR band in the same manner as for alkyl substituted compounds **1a-g**, it appeared that the equation which gives the best fit to Hammett $\sigma_{\text{m/p}}$ values could include all 12 compounds from **2a-f** and **3a-f** series. The corresponding correlation is given in Eq. (4):

$$\nu_{\text{NH}}^{4,6} = (-219.14 \pm 6.59)\sigma_{\text{m/p}} + (3067.00 \pm 3.06) \quad (4)$$

$$R = 0.995, s = 8.45, n = 12, F = 110.48$$

Except for the high standard deviations, the correlation according to Eq. (4) is satisfactory, but the correlation for both **2a-f** and **3a-f** series with F and R parameters is slightly less good considering the standard deviation (Eq. (5)):

$$\nu_{\text{NH}}^{4,6} = (-204.90 \pm 14.47)F + (-3219.45 \pm 12.88)R + (3066.48 \pm 7.33) \quad (5)$$

$$R = 0.994, s = 8.87, n = 12, F = 403.65$$

For the aryl substituted compounds, due to insolubility in DMSO- d_6 , only seven data on the chemical shifts of the NH bond from series **2a-f** and **3a-f** are available, but these gave a very good correlation as can be seen in Eq. (6):

$$\delta_{\text{NH}}^{4,6} = (0.277 \pm 0.04)\sigma_{\text{m/p}} + (12.56 \pm 0.02) \quad (6)$$

$$R = 0.961, s = 0.03, n = 7, F = 59.9$$

The correlation with F and R was also good (Eq. (7)):

$$\delta_{\text{NH}}^{4,6} = (0.245 \pm 0.04)F + (0.305 \pm 0.05)R + (12.57 \pm 0.02) \quad (7)$$

$$R = 0.977, s = 0.03, n = 7, F = 41.5$$

Good fit in the two last correlations, Eqs. (6) and (7), shows that the $^1\text{H-NMR}$ chemical shifts for the N–H bond, although the corresponding peaks are somewhat broad, are quite distinctive and seemingly free from any interferences.

The good correlations with the $^1\text{H-NMR}$ spectral data, led to the idea to check the validity of the method employed for selecting the IR bands most sensitive to the effect of substituents. Therefore, the values of the IR stretching frequencies and the available $^1\text{H-NMR}$ data were intercorrelated and the obtained correlation is presented in Eq. (8):

$$\delta_{\text{NH}} = (-0.00131 \pm 0.0001)\nu_{\text{NH}} + (15.69 \pm 0.54) \quad (8)$$

$$R = 0.957, s = 0.04, n = 7, F = 54.68$$

Considering that the determination of the $^1\text{H-NMR}$ chemical shifts is much more precise than that of the IR stretching frequencies, particularly because of the broad multiple NH band, this fairly good intercorrelation proves that the selection of the IR NH stretching frequencies for use in the correlations presented in this paper was justified.

It was taken for granted that 2-pyridone in the solid state is in the oxo-form and, on the basis of crystallographic data, mostly as a dimer. Hence, the IR spectra in KBr were treated accordingly. In solution, a tautomeric equilibrium exists,^{2,3} which has been extensively investigated.⁴ It was recently confirmed that 2-pyridone in the gaseous phase also exists as a dimer of both tautomeric forms, 2Py·2HP, resulting from a double proton transfer.⁵ However, the IR spectrum of 3-nitro-2-pyridone in KBr published in a Japanese database¹⁴ was declared as belonging to 3-nitro-2-hydroxypyridine, and had a distinctive hydroxy absorption band at 3432 cm^{-1} . In the same database, as mentioned previously, the unsubstituted 2-pyridone is presented as being exclusively in the oxo-form. This example shows that electronic effects drastically influence the existence of tautomeric forms, even in the solid state. This effect is particularly strong in the above-mentioned 3-nitro-2-pyridone,¹⁴ because the electron attracting nitro group in this compound is directly attached to the pyridone nucleus, as opposed to the compounds investigated in this paper, where the phenyl group is interpolated between the substituent and the pyridone ring, weakening the strong-electron accepting effects.

In the light of these data, it is also possible that the high standard errors in the presented calculations, in addition to resulting from the large numerical diffe-

rence between the two correlated values, $\sigma_{m/p}$ and the IR stretching frequencies, could also be due to some contribution of the 2-hydroxypyridine, which might also be the reason for the dispersion of the values of IR stretching frequencies of the nitro-substituted derivatives and the high standard deviations. It is possible that strong electron-attracting groups in the *p*- and *o*-position of the phenyl ring weaken the NH bond and facilitate a proton transfer to the carbonyl oxygen.

CONCLUSION

This paper presents the results of an LFER analysis of substituent effects on the IR stretching frequencies of the NH group and $^1\text{H-NMR}$ chemical shifts for three series of 4,6-disubstituted-3-cyano-2-pyridones. It was established that satisfactory correlations could be obtained with simple Hammett type parameters. Correlations with the Swain–Lupton constants yielded equations of similar precision.

It appears that electronic effects of both alkyl and aryl substituents considerably influence the spectral characteristics of the NH bond. It was not necessary to include steric parameters in the calculations to improve the correlations, as was previously necessary.¹ This is probably due to better transmission of substituent effects to the NH bond *via* the direct conjugation from the substituted phenyl group in position 4 and the negligibly small steric interaction of the substituent in position 6 with the practically linear N–H group. The substituent effects are therefore stronger and less affected by non-planarity of the pyridone nucleus and steric hindrance as was the case for CN, CO and 5H in a previous investigation.¹

The importance of a better knowledge of the effects of substituents on the NH bond, particularly in a view of the potential use of substituted 2-pyridones as therapeutic agents and DNA base mimics should be stressed.

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ИЗВОД

КОРЕЛАЦИОНА АНАЛИЗА IR И $^1\text{H-NMR}$ СПЕКТРАЛНИХ ПОДАТАКА ЗА NH ВЕЗУ У АЛКИЛ И АРИЛ 4,6-ДИСУПСТИТУИСАНИМ 3-ЦИЈАНО-2-ПИРИДОНИМА

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У раду је разматран утицај супституената на IR фреквенције и $^1\text{H-NMR}$ хемијска померања за пиридонску NH групу у 4- и 6-дисупституисаним алкил и арил 3-цијано-2-пиридонима коришћењем принципа линеарне корелације слободне енергије. За израчунавања су примењене Хаметове $\sigma_{m/p}$ константе као и Swain–Lupton константе супституената *F* и *R*. Развијен је компјутерски метод за избор IR NH трака најосетљивијих на утицај супституената.

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