EFFECT OF SUBSTITUENTS ON THE ^{1}H AND ^{13}C NMR CHEMICAL SHIFTS OF *trans*-PYRIDINEACRYLIC AND SUBSTITUTED *trans*-CINNAMIC ACIDS

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Abstract — The principles of linear free energy relationships were applied to the ^{1}H nmr and ^{13}C nmr chemical shifts induced by substituents in three isomeric *trans*-pyridineacrylic and substituted *trans*-cinnamic acids. The data for the carboxy proton chemical shift correlated well with the simple Hammett equation. Taft's dual substituent parameter equation was used for the interpretation of the balance of the inductive and resonance effects through the ethylenic bond for the C_α and C_β ^{13}C nmr shift. Using the nuclear Overhauser method, the conformation of the carboxylic group in 2-pyridineacrylic acid was determined, and its unexpected behaviour in both ^{1}H nmr chemical shifts and in the previously studied reaction with diazodiphenylmethane was interpreted by the increased electron density in the π-electronic system favoured by the orbital symmetry of the part of the acid molecule.

INTRODUCTION

In our previous paper[1] we investigated the reactivity of *trans*-pyridineacrylic and substituted *trans*-cinnamic acids in their reaction with diazodiphenylmethane (DDM) in dimethylformamide at 30 °C, employing the well known uv spectrophotometric method.[2] On the basis of the reaction constant ρ_2, the effect of substituents on the observed rate of the reaction was discussed, and the calculated $\rho_2/\rho_1=\pi=0.407$ was taken as a measure of the attenuation of electronic effects through the ethylenic bond. The reaction constant ρ_1 has previously been determined for substituted benzoic and pyridinecarboxylic acids under identical reaction conditions.[3] The obtained π value is in good agrement with the value $\pi=0.39 \pm 0.03$, for substituted cinnamic and benzoic acids in protic and aprotic solvents.[4]

The effect of substituents on the ^1H nmr chemical shifts of H_α and H_β protons in substituted *trans*-cinnamic acids has been reported by Katritzky and Swinbourne.[5] On the basis of the determined chemical shifts of the H_α protons and the known substituent constants σ , these authors calculated the corresponding ρ value, which was further used to calculate the σ values for aza- and modified aza-substituents from the determined ^1H nmr shifts for the H_α protons in pyridine and *N*-oxypyridineacrylic acids.[5]

RESULTS AND DISCUSSION

In the present paper we determined the effect of the substituents on the ^1H nmr chemical shifts of the ethylenic protons and carboxylic group protons, and also on the ^{13}C nmr chemical shifts for the C_α and C_β of the ethylene group in substituted *trans*-cinnamic and three isomeric *trans*-pyridineacrylic acids.

The general formula of the investigated acids is as follows:

$$X\text{-}C_6H_4\text{-}CH{=}CH\text{-}COOH$$

where X stands for H, *p*-Cl, *m*-Cl, *p*-NO_2, *m*-NO_2, 2N, 3N and 4N.

In the Table the values for the ^1H nmr chemical shifts for H_α, H_β and the carboxy proton are given, together with the ^{13}C nmr chemical shifts for the C_α and C_β of the ethylene group. For comparison, the corresponding rate constants for the reaction of the same acids with DDM in DMF[1] are included in the Table. Appropriate σ constants were taken from the literature.[5,6]

The ^1H nmr chemical shift for the H_α and H_β protons in the Table are in excellent agreement with the previously published data by Katritzky and Swinbourne.[5] The calculated coupling constants J_{H_α,H_β} are in the range 15.56-16.17 Hz, verifying the *trans*-configuration of the investigated acids.

The obtained chemical shift for the carboxy proton could be correlated by the Hammett equation in the form (1) :

$$\delta_{(H)X} = \rho \cdot \sigma_X + \delta_{(H)H} \qquad (1)$$

where $\delta_{(H)X}$ stands for the chemical shift caused by a substituent in the aromatic or heteroaromatic nuclei, $\delta_{(H)H}$ for the chemical shift for the unsubstituted acid, cinnamic acid (x=H), ρ is the measure of the succeptibility of the chemical shift for the carboxy proton to substituent effects, and σ is the corresponding substituent constant.

Table. ^{1}H Nmr and ^{13}C nmr chemical shifts[a] of *trans*-pyridineacrylic and substituted *trans*-cinnamic acids in DMSO-d_6

X	δH_α	δH_β	δ_{COOH}	δC_α	δC_β	$k_2 \times 10^{-4}$ $dm^3 mol^{-1} s^{-1}$
H	6.54	7.60	12.43	119.26	143.92	2.62
p-Cl	6.56	7.58	12.48	120.07	142.50	3.32
m-Cl	6.62	7.57	12.52	120.97	142.30	4.12
p-NO_2	6.74	7.69	12.70	123.61	141.32	7.42
m-NO_2	6.71	7.69	12.62	122.27	141.30	5.80
2N	6.82	7.59	12.59	122.65	143.17	4.02
3N	6.68	7.63	12.57	121.24	140.61	5.02
4N	6.79	7.56	12.72	123.13	141.23	7.94

a) in ppm relative to TMS

The obtained linear relationship for the carboxy proton is as follows (2) :

$$\delta_{(COOH)X} = 0.254\sigma_X + 12.43 \quad (r=0.837, s=0.06, n=8)^* \qquad (2)$$

If the deviating 2-pyridineacrylic acid is excluded, a better correlation is obtained :

$$\delta_{(COOH)X} = 0.343\sigma_X + 12.41 \quad (r=0.960, s=0.03, n=7) \qquad (3)$$

It is evident that the determined chemical shift for 2-pyridineacrylic acid is lower than predicted by its σ constant, considering the vicinity of the ring nitrogen. The lower reactivity of this acid is also seen in reaction with DDM (Table). Both phenomena indicate a higher electron density in the environment of the carboxylic proton. To obtain a better insight into the conformation of 2-pyridineacrylic acids, we used the well known nuclear Overhauser enhancement (NOE) method.

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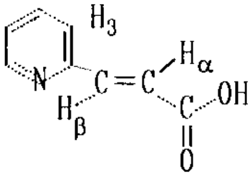
* r-correlation coefficient; s-standard deviation of ρ; n-number of points

The conclusions obtained from the (NOE) difference spectra are as follows. Irradiation of the H_α proton (6.82 ppm) brings about a more intense signal from the H_3 proton of the pyridine ring by 9%. If however the H_3 proton of the pyridine ring is irradiated, the increase of the H_α signal amounts to 18%, which proves that in the favoured conformation these nuclei are near one other. This conformation is further proved by a NOE signal of only 3% for the H_3 proton if the H_β proton is irradiated under the same condition, which confirms that H_3 and H_β are further apart. Irradiation of the carboxy proton gives the NOE signal twice as large as experienced by the H_α proton (6%), than by the H_β proton (3%). Therefore, the conformation of 2-pyridineacrylic acid could be written as follows:



Investigation of the reaction of pyridineacrylic acids with DDM in DMF established lower reactivity than expected for this acid.[1] It is evident from the data presented in this work that the ^1H nmr chemical shift is low considering the relatively close proximity of the ring nitrogen. The extended delocalised π-electronic system which is operative in the transmission of substituent effects is the same in all the investigated molecules, but it is only in the 2-pyridineacrylic acid that some degree of orbital symmetry could be visualized for the part of the molecule terminated by the ring nitrogen and the carboxylic group. These terminal groups also possess orthogonal p-orbitals, lone pair orbitals on the ring nitrogen and carbonyl oxygen of the carboxylic group, or pseudo-orthogonal p-orbital of the hydroxyl oxygen. Now, it may seem fairly far-fetched to ascribe orthogonality to the hydroxyl group orbitals, but this is taken for granted for the carboxylate anion. It has already been suggested on the basis of available data,[1,3] (and references therein) that the transition state in the reaction with DDM in aprotic solvents and therefore in DMF as well, leads to an ion-pair intermediate (Scheme).

$$\mathrm{RCOOH} + \mathrm{Ph_2CN_2} \xrightarrow{\text{slow}} \mathrm{RCOO^-\,Ph_2CN_2H^+}$$

$$\mathrm{RCOO^-\,Ph_2CN_2H^+} \xrightarrow{\text{fast}} \mathrm{RCOO^-\,Ph_2CH^+} + \mathrm{N_2}$$

$$\mathrm{RCOO^-\,Ph_2CH^+} \xrightarrow{\text{fast}} \mathrm{RCOOCHPh_2}$$

Scheme. Mechanism of the reaction of carboxylic acids with diazodiphenylmethane in DMF.

Therefore any increase in the electron density of the system should be expected to lower the reactivity of the carboxylic proton. A similar explanation could be given for the ^{1}H nmr chemical shift lower than expected, although the perturbation is not proportional. This is indicated by an excellent intercorrelation of the log rate constants in the reaction with DDM and the ^{1}H nmr chemical shifts of the carboxy proton, if the data for 2-pyridineacrylic acid are excluded :

$$\log k_{2\,(DDM)} = 1.83 \times 10^{-3} \delta_{COOH} - 2.25 \times 10^{-3} \quad (r=0.998,\ s=0.01,\ n=6) \qquad (4)$$

This shows that in all the other investigated molecules, the transmission of substituent effects is practically identical for both observed phenomena, as could have been expected.

The most interesting substituent effects were observed on the basis of the ^{13}C nmr chemical shifts of the ethylenic bond C_α and C_β carbons in the investigated acids. The data in the Table show that all aromatic ring substituents cause an increase of the electron density at the C_β (upfield shift), while the same substituents decrease the electron density at the C_α (downfield shift). Insertion of the available data into the Hammett equation of the mentioned type (1), gives the following relationships (5) :

$$\delta_{(C\alpha)} = 4.96\sigma + 119.03 \quad (r = 0.957,\ s = 0.50,\ n=7) \qquad (5)$$

$$\delta_{(C\beta)} = -3.28\sigma + 143.51 \quad (r = 0.903,\ s = 0.52,\ n=7)$$

Although the value of correlation coefficient for the C_β atom is not satisfactory, it should be noted that ρ for C_α is positive, while that for C_β is negative. There is no doubt that there is an alternation of polar effects in the conjugated system of investigated acids. Similar effects were observed in other conjugated systems, substituted 1-phenyl-1,3-butadienes and phenylallenes,[7] 1-phenylpropynes and 1-phenylpropenes,[8] as well as in ring substituted styrenes[9] and 3-aryl-2-cyanoacrylamides.[10]

The effects of substituents in the aromatic ring on the ^{13}C nmr chemical shifts is customarily analysed using Taft's Dual-Substituent Parameter equation. We used this equation in the following form:

$$\delta_X = \rho_I \sigma_I + \rho_R \sigma_R + \delta_H \qquad (6)$$

where δ_X and δ_H are the corresponding chemical shifts caused by the substituent X and in the unsubstituted molecule, respectively, ρ_I and ρ_R measure the sensitivity of the chemical shifts to the inductive and resonance effects of the substituents, and σ_I and σ_R are substituent constants reflecting the inductive and resonance effects, respectively.

Application of the multiple linear regression analysis to the obtained data using equation (6) yields the following relationships (7) :

$$\delta_{(C\alpha)x} = 4.37\,\sigma_I + 6.39\,\sigma_R + 119.39 \quad (r=0.969, s=0.48, n=7) \tag{7}$$

$$\delta_{(C\beta)x} = -\,4.31\,\sigma_I - 1.41\,\sigma_R + 143.99 \quad (r=0.946, s=0.45, n=7)$$

The values for σ_I and σ_R employed in equation (6) were taken from the literature,[11] and are as follows: σ_I = 0.47 (*m*- and *p*-Cl), σ_R = -0.24 (*p*-Cl), σ_R =- 0.08 (*m*-Cl), σ_I = 0.63 (*m*- and *p*-NO_2), σ_R = 0.15 (*p*-NO_2) and σ_R = 0.05 (*m*-NO_2). By analogy, the values of σ_I for 3N and 4N are 0.6, while $\sigma_{R\ (3N)}$ =0, $\sigma_{R\ (4N)} = \sigma_{4N} - \sigma_{3N}$ = 0.8 - 0.6 = 0.2.

From the coefficients in equation (7) it could be concluded that the C_α atom of the ethylenic group is influenced not only by the inductive (ρ_I= 4.37) but also, to an even bigger extent, by the resonance effect (ρ_R=6.39). The ratio $\rho_R / \rho_I = \lambda$ amounts to 1.46 which is very close to the ratio $\lambda=\rho_R/\rho_I$=1.51, established for substituted styrenes.[9] This indicates the similarity in the transmission of substituent effects from the aromatic ring to the ethylenic C_α of the investigated acids and on the C_β atom in substituted styrenes.* Exceptionally good intercorrelation was obtained between ^{13}C nmr chemical shifts for the C_β atom in substituted styrenes[12] and ^{13}C nmr chemical shifts of the C_α atoms in the substituted cinnamic and pyridineacrylic acids with the same substituents in DMSO-d_6 which were the subject of the present study:

$$\delta_{(C\alpha)acid} = 0.844\,\delta_{(C\beta)styrene} + 23.00 \quad (r = 0.999, s=0.09, n = 5) \tag{8}$$

This confirms the similarity in the transmission of electronic effects of substituents from the aromatic ring to the observed carbon atom in the side chain.

As far as the effects of the supstituents on the C_β atom are concerned, it is evident that the inductive effect is far more pronounced (ρ_I=-4.31) as compared to the resonance interaction, (ρ_R=-1.41). The ratio $\lambda=\rho_R/\rho_I$ =0.32 is higher than the corresponding ratio for the C_α atom in substituted styrenes, where it is only 0.08.[9] The reason for this could be the more extended delocalised π-electronic system, which favours transmission via the resonance effect. However, it is also possible to obtain a successful intercorrelation for this particular C atom between the ^{13}C nmr chemical shift in substituted styrenes[12] and in the acids examined in this work :

$$\delta_{(C\beta)acid} = 1.385\,\delta_{(C\alpha)styrene} - 45.27 \quad (r=0.981, s=0.24, n = 5) \tag{9}$$

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* In substituted styrenes the carbon atom closer to the aromatic nucleus is designated C_α, while the terminal C atom is C_β. The designation is reversed in the investigated acids.

which exemplifies a similar mechanism and proportionality in the transmission of electronic effects from the substituted aromatic nucleus to the side-chain in both systems.

EXPERIMENTAL

All the investigated acids were synthesized by the piperidine catalyzed reaction of malonic acid and the corresponding benzaldehyde or pyridinaldehyde in pyridine solution and had melting points in agreement with those in the literature.[1]

The ^{1}H nmr spectra were obtained in deuterated dimethyl sulfoxide (DMSO-d_6) with tetramethylsylane (TMS) as the internal reference signal using a Bruker AC 250 E spectrometar operating at 250 MHz and room temperature. The ^{13}C nmr spectra were measured at 62.9 MHz with the same instrument.

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