

CONTRIBUTION TO THE STUDY OF INDUCTIVE EFFECT TRANSMISSION IN PYRROLE DERIVATIVES

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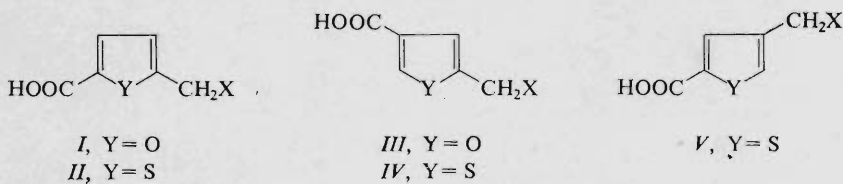
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Transmission of the inductive effect in pyrrole derivatives was investigated on 2-ethylpyrrole (VIa), 2-methylpyrrole (VIb), 2-dimethylaminomethylpyrrole (VIc), 2-hydroxymethylpyrrole (VI d), methyl 2-pyrrolylacetate (VIe), 2-pyrrolylacetonitrile (VI f), 2-benzenesulfonylmethylpyrrole (VIg) and trimethyl(2-pyrrolylmethyl)ammonium iodide (VIh), by comparison of their relative basicities and acidities. These were determined by IR spectroscopy from the strength of donor-acceptor interactions of the pyrrole derivatives with suitable standard compounds. The found differences show good linear correlations with the σ_1 substituent constants. On this basis, the transfer of the inductive effect in the given pyrrole series appears to be proportional.

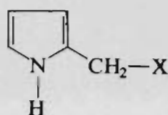
A suitable model for study of the inductive effect transmission in aromatic systems was introduced by Exner who utilized a series of *p*-toluic acids with substituents on the methyl group¹; the mesomeric effect in this type of compounds was eliminated by the CH₂ group. Transmission of inductive effect in the furan and thiophene series^{2,3} was studied using the analogous types I to V. Substitution effects in these



models were followed using pK values and C=O vibration frequencies in substituted carboxylic acids. In all series a proportional transmission of the inductive effect was found. Comparison of furan, thiophene and benzene models has shown that the extent of the transmission decreases in the mentioned order. An analogous decrease was found for the series II, IV and V. This order is caused by a decreased mobility of π -electrons, supporting thus the assumption of inductive effect transmission

through the σ -bonds as well as with participation of π -electrons. No similar approach has been applied as yet to the pyrrole series. Some studies (such as ref.⁴⁻⁶) investigated both the inductive and the mesomeric effects of substituents on the pyrrole nucleus.

The present communication represents an application of the Exner's benzylic model to the pyrrole series. The pyrrole nucleus itself already contains a significant acidobasic center which could be utilized for the study of substituent effects; this enables us to use structurally simpler compounds of the type VI. Because of difficult preparation of simple halogeno derivatives of pyrrole, we tried to prepare the required derivatives *via* the dimethylaminomethyl derivative VIc or its methoiodide VIh.



- VIa, X = CH₃
 VIb, X = H
 VIc, X = N(CH₃)₂
 VI d, X = OH
 VIe, X = COOCH₃
 VI f, X = CN
 VI g, X = SO₂C₆H₅
 (+)
 VI h, X = N(CH₃)₃

In addition to the already described nucleophilic reactions with OH⁽⁻⁾ and CN⁽⁻⁾ anions, the compound VIh reacted with sodium benzenesulfinate to give the benzene-

TABLE I

Values of $\Delta\nu(\text{THF})$ and $\Delta\nu(\text{CDCl}_3)$ according to the relationship (1) and (3), and wavenumbers of stretching vibrations of non-associated bonds N—H ($\nu_{\text{N-H}}^{\text{non-assoc}}$) for the pyrrole derivatives VI

Compound	$\Delta\nu_{\text{THF}}, \text{cm}^{-1a}$	$\Delta\nu_{\text{CDCl}_3}, \text{cm}^{-1b}$	$\nu_{\text{N-H}}^{\text{non-assoc}}, \text{cm}^{-1c}$
VIa	164	10	3 483
VIb	160	11	3 483
VIc	169	10	3 473
VI d	183	8 ^d	3 478
VIe	^e	10	3 461
VI f	194	8	3 468
VI g	190	0 ^f	3 457
VI h	188 ^g	0 ^f	^h

^a Mean accuracy $\pm 2 \text{ cm}^{-1}$; ^b mean accuracy $\pm 1 \text{ cm}^{-1}$; ^c mean accuracy $\pm 2 \text{ cm}^{-1}$; ^d lower reading accuracy; ^e the spectrum of VIe with tetrahydrofuran was not reproducible; ^f the bands due to associated and non-associated bonds were not separated; ^g not well determinable value; because of its lower accuracy it was not used in the correlation; ^h compound VIh is insoluble in CCl₄.

sulfonyl derivative *VIg*. Nucleophilic substitutions, leading to compounds *VI f* and *VIg*, were performed in dimethylformamide as the solvent of choice. Other attempted nucleophilic substitutions, known to take place with gramine, such as e.g. with $\text{CH}_3\text{O}^{(-)}$ or $\text{C}_6\text{H}_5\text{O}^{(-)}$ anions, led only to complex mixtures of products.

Pyrrole and its homologues are very weak bases and the corresponding dissociation constants cannot be therefore determined by titration; even the determination by UV spectroscopy is not without problems⁸. We used therefore IR spectroscopy for our study⁹. The differences in the relative acidities or basicities were determined as changes in the strength of hydrogen bonds between the studied compounds and a standard proton acceptor (the pyrrole N—H bond as the proton donor) or a standard proton donor (the pyrrole N-atom as proton acceptor).

As a suitable proton acceptor we chose tetrahydrofuran (THF). The values of $\nu_{\text{N-H}}^{\text{assoc}}$ decrease with increasing strength of the N—H...O (THF) hydrogen bond which is proportional to the relative acidity in the series of derivatives. Table I lists the $\Delta\nu_{\text{THF}}$ values, defined by the equation

$$\Delta\nu_{\text{THF}} = (\nu_{\text{N-H}}^{\text{non-assoc}})^0 - \nu_{\text{N-H}}^{\text{assoc}} \quad (1)$$

which relate the wavenumber decrease to the standard value for the non-associated N—H bond of the derivative *VIb*, where X = H ($\sigma_1 = 0.00$). The $\Delta\nu_{\text{THF}}$ values

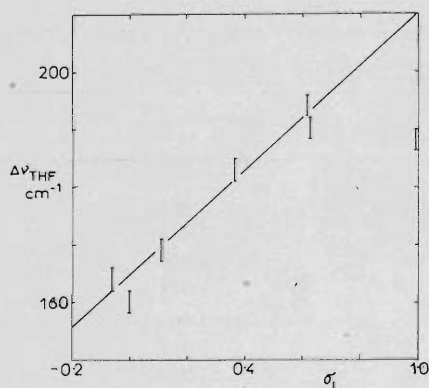


FIG. 1

Plot of $\Delta\nu(\text{THF})$ against the σ_1 substituent constants for derivatives *VI*. Linear relationship according to equation (2). The abscisses show the accuracy of $\Delta\nu(\text{THF})$ values.

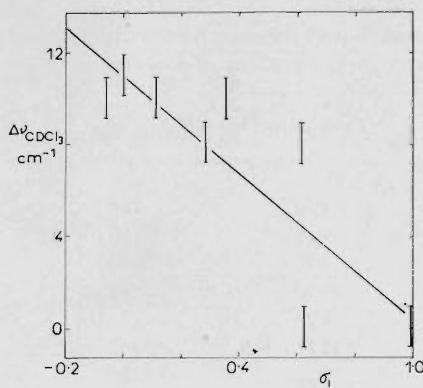


FIG. 2

Plot of $\Delta\nu(\text{CDCl}_3)$ values against the σ_1 substituent constants for derivatives *VI*. Linear relationship according to equation (4). The abscisses show accuracy of the $\Delta\nu(\text{CDCl}_3)$ values.

exhibit a linear dependence on the σ_I values (Fig. 1). The pertinent correlation equation is

$$\Delta\nu_{\text{THF}} = 46.13\sigma_I + 164.7 \text{ (cm}^{-1}\text{)}. \quad (2)$$

The correlation coefficient is high ($r = 0.966$; for the 99% significance level $r = 0.91720$ and for the 99.9% level $r = 0.97406$).

For the study of relative basicities in the series of pyrrole derivatives we used deuteriochloroform as proton donor (no reproducible spectra were obtained with phenol). The differences $\Delta\nu_{\text{CDCl}_3}$ in Table I are defined as

$$\Delta\nu_{\text{CDCl}_3} = \nu_{\text{C-D}}^{\text{non-assoc}} - \nu_{\text{C-D}}^{\text{assoc}}. \quad (3)$$

This relation, analogous to equation (1), gives information about the strength of the interaction $\text{C}=\text{H}\cdots\text{N}$ in the pyrrole derivatives. The thus-expressed differences in basicity can again be correlated with the σ_I substituent constants. The least squares method afforded the equation

$$\Delta\nu_{\text{CDCl}_3} = -10.58\sigma_I + 10.96 \text{ (cm}^{-1}\text{)}, \quad (4)$$

which is depicted in Fig. 2. Its lower correlation coefficient, $r = 0.841$ (99% significance level), corresponds to the greater scatter of the experimental points. Nevertheless, the decrease in basicity with increasing σ_I values is undisputable and in accord with the same direction of the acidity increase, found with tetrahydrofuran.

The σ_I constants can also be correlated with the vibrations of non-associated N—H bonds in pyrrole derivatives in tetrachloromethane solutions. The calculated linear relationship

$$\nu_{\text{N-H}}^{\text{non-assoc}} = -31.4\sigma_I + 3480 \text{ (cm}^{-1}\text{)} \quad (5)$$

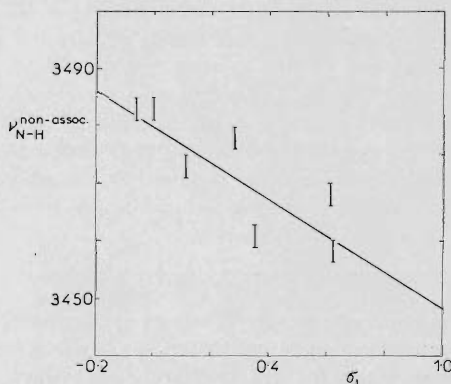


FIG. 3

Plot of stretching vibrations of the non-associated N—H bonds in pyrrole derivatives $\nu_{\text{N-H}}^{\text{non-assoc}}$ against the σ_I substituent constants.

Linear relationship according to equation (5). The abscisses show accuracy of the $\nu_{\text{N-H}}^{\text{non-assoc}}$ values.

is depicted in Fig. 3. Its correlation coefficient corresponds to 98% significance level, $r = 0.833$.

The experimental data thus show a proportional transmission of the inductive effect in the pyrrole system.

EXPERIMENTAL

The boiling and melting points are uncorrected. Solid analytical samples were dried at 7 Pa for 24 h. $^1\text{H-NMR}$ spectra were measured on a Varian XL 100 (100 MHz) instrument; chemical shifts are given in the δ scale (relative to tetramethylsilane). Mass spectra were measured on a Gas Chromatograph-Mass Spectrometer LKB 9000 instrument, IR spectra on a Zeiss UR-20 spectrophotometer. Association of the compounds with tetrahydrofuran was measured both in a binary system (in tetrahydrofuran) and in a ternary mixture (in a 1 : 1 mixture of tetrahydrofuran and tetrachloromethane). The measurements of hydrogen bonds with deuteriochloroform were performed in solutions of concentrations 2.5 mol l^{-1} .

Compounds *VIa* and *VIb* were prepared by the described¹⁰ procedure from 2-acetylpyrrole¹¹ and 2-pyrrolecarbaldehyde¹², respectively. The derivative *VIc* was synthesized also from 2-pyrrolecarbaldehyde¹³. Compounds *VIc* (ref.¹⁴), *VIc* (ref.¹⁵), *VIc* (ref.¹⁶) and *VIh* (ref.¹⁶) were obtained by described procedures. The ester *VIe* was prepared by reaction of 2-pyrrolylacetic acid with an equivalent quantity of ethereal diazomethane.

2-Pyrrolylacetic Acid

A mixture of 2-pyrrolylacetonitrile (*VIc*; 2.24 g; 20 mmol), potassium hydroxide (3 g), water (15 ml) and methanol (5 ml) was refluxed for 1.5 h, cooled, extracted with ether ($2 \times 30 \text{ ml}$) and the aqueous layer was acidified with concentrated hydrochloric acid (pH 1). The product was taken up in ether ($5 \times 15 \text{ ml}$), the combined ethereal extracts were dried over anhydrous magnesium sulfate and taken down, leaving 1.7 g (68%) of the crude acid which on crystallization from ethanol melted at $82-83^\circ\text{C}$ (reported¹⁷ m.p. $83-84^\circ\text{C}$).

2-Pyrrolylacetonitrile (*VIc*)

A mixture of the quaternary iodide *VIh* (13.3 g; 50 mmol), dimethylformamide (50 ml) and sodium cyanide (7 g; 143 mmol) was heated on a steam bath under stirring for 2 h. After standing for 1 h and cooling, water (100 ml) was added and the solution was extracted with ether ($4 \times 30 \text{ ml}$). The combined ethereal solutions were dried over magnesium sulfate, taken down and the residue was distilled *in vacuo*. The fraction, boiling at $88-90^\circ\text{C}/13 \text{ Pa}$ (reported¹⁶ b.p. $102-103^\circ\text{C}/147 \text{ Pa}$), consisted of the pure nitrile *VIc*; yield 3.6 g (64%). The possible rearrangement product, 2-cyano-5-methylpyrrole, was not detected. When the reaction was performed in an aqueous medium, the reported¹⁶ yield was lower than 50%.

2-Benzenesulfonylmethylpyrrole (*VIg*)

A mixture of the salt *VIh* (6.65 g; 25 mmol), sodium benzenesulfinate (16 g; 80 mmol) and dimethylformamide was heated on a steam bath under stirring for 3 h. After cooling, water (50 ml) was added and the mixture was extracted with ether ($4 \times 20 \text{ ml}$). The combined ethereal extracts were washed with water (30 ml), dried over magnesium sulfate and taken down. The

residue was crystallized from ethanol, m.p. 122–124°C. For $C_{11}H_{11}NO_2S$ (221.3) calculated: 59.71% C, 5.01% H, 6.33% N, 14.49% S; found: 59.95% C, 5.08% H, 6.57% N, 14.45% S. 1H -NMR spectrum ($CDCl_3$, ppm): 4.37 (s, 2 H), 5.76 (m, 1 H), 6.04 (dd, 1 H, $J_{3,4} = 4$ Hz, $J_{4,5} = 2$ Hz), 6.80 (m, 1 H), 7.52 (m, 5 H), 8.5–9.4 (s br, 1 H); IR spectrum ($CHCl_3$, cm^{-1}): 806 w, 877 w, 1 030 m, 1 081 s, 1 128 s, 1 150 s, 1 308 s, 1 315 s, 1 448 s, 1 588 w, 3 010 w, 3 380 w, 3 470 s.

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