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Reactivity of Pyrrole Pigments, 4. Part[1]: Deuteration of 5-Arylmethylene-3-pyrrolin-2-ones with d_1-Trifluoroacetic Acid

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5-Arylmethylene-3,4-dimethyl-3-pyrrolin-2-ones on treatment with d_1-trifluoroacetic acid (d_1-*TFA*) undergo deuterium substitution at the carbon atom of the methylene bridge. This electrophilic substitution is related to similar deuteration reactions of verdins (bilatrienes-a,b,c). The results obtained can be interpreted by a free energy relationship, assuming that the field effect, becomes negligible by the influence of *TFA*.

(Keywords: Bile pigments; Deuteration; Trifluoroacetic acid; Field effect; FMMF method)

Reaktivität von Pyrrolpigmenten, 4. Mitt.:
Deuterierung von 5-Arylmethylen-3-pyrrolin-2-onen mit d_1-Trifluoroessigsäure

Bei Behandeln mit d_1-Trifluoroessigsäure (d_1-*TFA*) werden 5-Arylmethylen-3-pyrrolin-2-one am Kohlenstoffatom der Methylenbrücke deuteriert. Ähnliche elektrophile Substitutionsreaktionen findet man in der Klasse der Verdine (Bilatriene-a,b,c). Die experimentellen Ergebnisse können mit Hilfe einer linearen Freien Energie Beziehung unter der Annahme interpretiert werden, daß der Feldeffekt durch den Einfluß von *TFA* vernachlässigbar wird.

Introduction

In a previous paper we described the reaction of 5-arylmethylene-3-pyrrolin-2-ones and pyrromethenones with cyanide ion to give the corresponding cyanomethylenepyrrolidin-2-ones[2]. The site where this nucleophilic attack takes place is predicted by the reactivity indexes calculated from Fukui's frontier orbital model[2,3]. The same model predicts that an electrophilic reagent will also attack at the bridge

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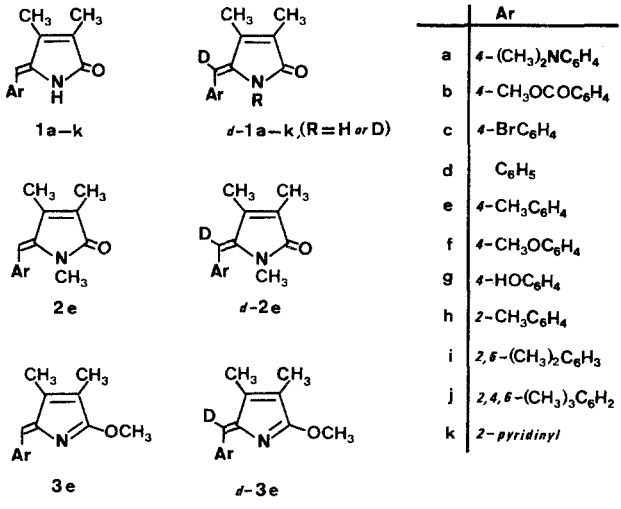
carbon atom. In this paper we discuss the behaviour, of 5-arylmethylene-3,4-dimethyl-3-pyrrolin-2-ones, **1a–k**, **2e** and the lactim form of the last, **3e** (see Scheme 1), in presence of deuterated trifluoroacetic acid (d_1-*TFA*). This is a first step in the study of the reactivity towards electrophiles of arylmethylene-3-pyrrolin-2-ones and pyrromethenones, both of which are partial models for verdins (bilatrienes-a,b,c) and rubins (biladienes-a,c).

Results and Discussion

Upon treatment with d_1-*TFA* at 60°, compounds **1a–k**, **2e** and **3e** afford the corresponding products in which the hydrogen atom on the methylene bridge has been substituted by deuterium: *d*-**1a–k**, *d*-**2e** and *d*-**3e** (see Scheme 1). Table 1 shows the observed rate constants for

Scheme 1



0.2 *M* solutions in d_1-*TFA* at 60° (see Exp. Part for details). Obviously under this conditions the exchange of the lactam proton occurs even faster; on the other hand, substitution of aromatic hydrogens is only observed for the 2,4,6-trimethylphenyl derivative **1j**. Owing to the general instability of pyrromethenones in strong acidic media, it is not possible to perform a parallel study of this reaction with them. However, a similar electrophilic substitution reaction has been descri-

bed, in which the deuteration of bilatrienes-a,b,c takes place at the outer bridge positions (C-5 and C-15)[4,5].

The reported results point out the mechanisms shown in Scheme 2 as the more reasonable ones.

2e ($R=CH_3$) has a larger rate constant as **1e** ($R=H$) (see Table 1) according to the reaction path $A \rightarrow Int^+ \rightarrow B$. In contrast, the effect of a substituent at *para* position of the phenyl ring (for compounds **1a-g**) is

Scheme 2

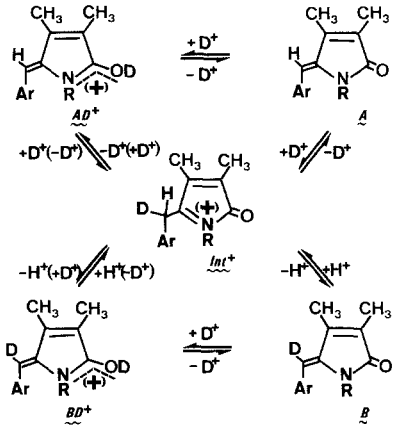


Table 1. *Proton to deuterium exchange at the methine carbon of 5-ylidene-3-pyrrolin-2-ones* (**1a-i**, **1k**, **2a** *and* **3a**); *0.2 M solutions in* d_1*-TFA at 60°*

Compound	Rate constant[a] $k \cdot 10^3$ (s^{-1})	$\log k_x/k_{\mathbf{1d}}$
1a	3.00 ± 0.12	−0.09
1b	4.81 ± 0.21	0.12
1c	3.19 ± 0.15	−0.06
1d	3.67 ± 0.19	0.00
1e	3.44 ± 0.24	−0.03
1f	2.17 ± 0.08	−0.23
1g	2.27 ± 0.40	−0.21
1h	3.03 ± 0.04	−0.08
1i	3.22 ± 0.20	−0.06
1k	1.44 ± 0.05	−0.41
2e	3.83 ± 0.50	0.02
3e	3.48 ± 0.35	−0.02

[a] Determined by ^{1}H-NMR (60 MHz; see Exp. Part).

not easy to explain. For example, any attempt to verify a linear free energy relationship by using the *Hammett* constant σ_p[6] fails, since the plot of $\log k/k_{1d}$ *versus* σ_p results in a map of random points, and similar unsuccessful correlations are observed when σ_m[6] or σ_I[6] are used. Only when $\log k/k_{1d}$ is plotted *versus* σ_R[7] a straight line is observed (correlation coefficient = 0.96 and $\rho = 0.42 \pm 0.04$); Table 2 shows the constants used and Fig. 1 the result of plot $\log k/k_{1d}$ *versus* σ_R.

Table 2. *Values used for the substituent constants*[6,7] σ_p, σ_m, σ_I, *and* σ_R

Substituent	σ_p	σ_m	σ_I	$\sigma_R (= \sigma_p - \sigma_I)$
CH_3	−0.17	−0.07	-0.055 ± 0.005	-0.115 ± 0.05
Br	0.23	0.39	0.475 ± 0.025	-0.245 ± 0.025
OH	−0.37	0.12	0.265 ± 0.015	-0.635 ± 0.015
OCH_3	−0.27	0.12	0.280 ± 0.030	-0.550 ± 0.030
COOR	0.47	0.37	0.325 ± 0.025	0.145 ± 0.025
NH_3^+	0.82	0.88	0.955 ± 0.035	-0.135 ± 0.025

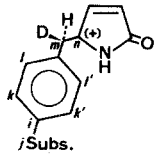
σ_R is calculated from $\sigma_R = \sigma_p - \sigma_I$ where σ_I accounts for the field effect of the substituent and σ_R for its total resonance contribution (i.e. σ—π, n—π and π—π).

The calculation—as well the corresponding diagrams—done by using the σ constant obtained from the Field-Mesomeric-Mesomeric Field (FMMF) model of *Dewar*[8] leads to the same result: only when the field effect is neglected, a linear relationship between $\log k/k_{1d}$ and the considered σ constant is found. Fig. 1 shows also the straight line that results using *Dewar*'s model, the correlation coefficient and the ρ value being practically the same as for the plot *versus* σ_R described above.

The FMMF model σ constant was calculated according to the following equation[8b]:

$$\sigma = -F\,(1/r_{in} - 0.9/r_{jn}) + M \cdot q_{im} - MF \cdot \sum_{k \neq m} q_{ik}/r_{kn} \qquad (1)$$

Scheme 3



in which the first term to the right represents the field effect contribution.

Distances r_{in}, r_{jn} and r_{kn} were estimated from standard bond lengths; q_{im} and q_{ik} are the negative formal charges at positions m and k of the alternant hydrocarbon anion (*Longuet-Higgins* method[8c]) resulting when it is assumed that "Subs." equals CH_2^-. Tables 3 and 4 summarize the values used for the set of parameters and for constants F, M, MF in the above equation. Localization of the positive charge on the nitrogen does not lead to significant differences in our calculations.

Table 3. *Values used for the parameters of equation (1)* [a, b] *in the FMMF method*[8]

	$1/r_{in}$	$0.9/r_{jn}$	$r_{k'n}$	r_{kn}	q_{im}	q_{ik} and $q_{ik'}$
para substitution	1/3.6	0.9/4.5	2.9	3.6	0.143	0.143
ortho substitution	1/2.7	0.9/3.0	2.9	3.6	0.143	0.143

[a] See text.
[b] Distances expressed in units of C—C benzene bond length (1.4 Å).

Table 4. *Values used for the constants F, M, and MF*[8] *for obtaining σ quantities*

Substituent	F	M	MF	σ (FMMF) total	σ (FMMF) without the field effect contribution
p-CH_3	—0.87	—0.91	—0.36	—0.23	—0.16
o-CH_3	—0.87	—0.91	—0.36	—0.23	—0.16
p-Br	4.92	—1.14	—0.30	0.38	—0.19
p-OH	2.48	—3.70	—0.59	0.19	—0.58
p-OCH_3	3.16	—3.14	—0.98	0.25	—0.54
p-COOR	3.18	0.93	0.49	0.25	0.18
p-$NH(CH_3)_2^+$ [a]	10.92	—0.40	—0.54	0.85	—0.11

[a] Calculated for NR_4^+ from the same constants and method[8] as for the rest of substituents.

These results, which are shown in Fig. 1 indicate that the effect of the substituent is only the stabilization of the initial species (AD^+ or/and A). This stabilization is due to delocalization of the π-electrons of the aryl group into the 5-methylene-3-pyrrolin-2-one unit; the higher the single bond character for the bonding between aryl group and bridge carbon atom, the smaller the energy difference between the initial species and the intermediate cation (Int^+) will be. However, this "resonance" between the aryl group and the 5-methylene-3-pyrrolin-2-one unit cannot be very large, since these two groups are not coplanar[9]. If this is true, an increase of the dihedral angle—as in the 2,6-dimethylphenyl derivative **1i**[10]—should result in an increase on the

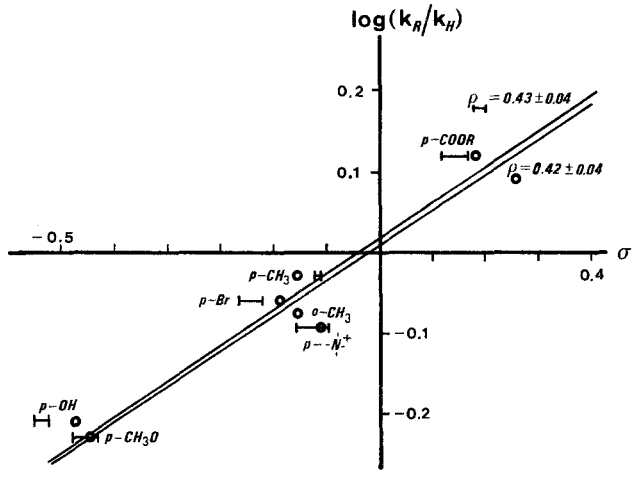


Fig. 1. Linear Free energy relationships for the deuteriation of 5-arylmethylene-3-pyrrolin-2-ones **1 a-i** and **1 k**: |—|, σ_R: ○, σ (FMMF) without field effect contribution

reaction rate (regardless of the steric hindrace). This prediction is in fact confirmed as indicated by comparison of the reaction rates of **1 e, 1 h** and **1 i**. The above observations also indicate that the conformation of linear bile pigments must have some influence on their reactivity. However, the substituent effect, through resonance stabilization of the initial species, can be an indication of a reaction path $AD^+ \rightarrow Int^+ \rightarrow BD^+$, with equal charged species and, consequently, with little influence of the field effect. But as well a reaction path $A \rightarrow Int^+ \rightarrow B$ with limiting reaction path on the formation of A due to the left displaced reaction equilibrium $AD^+ \rightleftharpoons A$ may be indicated. Nevertheless, this interpretation is not in agreement with the reaction constants of **1 a** and **1 k**, and therefore these compounds, in *TFA* solution, should exist either as a dication or as a monocharged species where the charge is not localized on the lactam ring. Another interpretation of this substituent effect can be made on the basis of the uncommon properties of *TFA* as solvent[11,12]; e.g. when compared to acetic acid, *TFA* has the ability to convert S_N2 solvolysis reactions in S_N1 type ones. *TFA* stabilizes carbocations but does not have nucleophilic character. A model for *TFA* has been proposed[11] where the carbonium ion stabilization occurs through the CF_3 group instead of the oxygen atoms.

Consequently there seems to be not much use in looking for a field effect for $Int^{\oplus}$ where the charge is delocalized throughout the entire π-system including the surrounding *TFA* solvent molecules.

Experimental

Melting points were determined on a *Kofler* (Reichert) microhot stage apparatus. Preparative thin layer chromatography (PTLC) was carried out on 20 × 20 cm plates using Merck 60 HF_{254} silica (1 mm thickness). All products separated by PTLC were subsequently purified by chromatography on a small column of Merck 60 silica. Infrared spectra (IR) were recorded on a Pye Unicam SP 1100 spectrometer, and mass spectra (MS) on a Hewlett-Packard 5700-A spectrometer. Proton magnetic resonance spectra (^{1}H-NMR) were determined with a Perkin-Elmer R 12 A instrument (60 MHz).

The preparation and properties of the following compounds are described in the literature: **1a**[13], **1c**[1], **1d**[14], **1e**[15], **1f**[1], **1g**[13], **1h**[1], **1k**[16], **2e**[17], **3e**[17].

(Z)-3,4-Dimethyl-5-(4-methoxycarbonylphenyl)methylene-3-pyrrolin-2-one (**1b**, $C_{15}H_{15}NO_3$)

The condensation of 3,4-dimethyl-3-pyrrolin-2-one with 4-formylbenzoic acid following the general procedure described in Lit.[15,18] yielded a crude reaction product (96%) consisting of sodium (*Z*)-4-(3,4-dimethyl-2-oxo-3-pyrroline-5-yliden)methylbenzoate. 1.37 g (5.2 mmol) of this sodium salt, dissolved in 400 ml anhydrous methanol containing 0.5 ml H_2SO_4 98%, were refluxed for 12 h. Neutralisation, evaporation of methanol and extraction of the aqueous phase with $CHCl_3$ afforded **1b** (463 mg; 34%); m.p. 219-221°.

^{1}H-NMR (δ, $DCCl_3$): 8.25 (broad, s, NH), 7.25 (m, aromatic H), 6.07 (slightly broad s, =CH—), 3.93 (s, CH_3O), 2.2 (sl. broad s, CH_3-4), 1.94 (sl. broad s, CH_3-3).

IR (cm^{-1}, KBr): 1710, 1690 (C=O).

(Z)-3,4-Dimethyl-5-(2,6-dimethylphenylmethylene)-3-pyrrolin-2-one (**1i**, $C_{15}H_{17}NO$)

Prepared (following the general procedure[15,18]) from 3,4-dimethyl-3-pyrrolin-2-one and 2,6-dimethylbenzaldehyde [the last was obtained by reduction of 2,6-dimethylbenzonitrile[19] with $LiAlH(C_2H_5O)_3$ according to the method described in[20,21]]; m.p. 151-154°.

^{1}H-NMR (δ, $CDCl_3$): 7.05 (s, aromatic H), 6.62 (broad s, NH), 6.05 (sl. broad s, =CH—), 2.21 (s, two aromatic CH_3), 2.14 (sl. broad s, CH_3-4), 1.90 (sl. broad s, CH_3-3).

IR (cm^{-1}, KBr): 1690 (C=O).

MS (*m*/e, 70 eV): 227 (M^+, 61%), 212 (28%), 198 (base peak).

(Z)-3,4-Dimethyl-5-(2,4,6-trimethylphenylmethylene)-3-pyrrolin-2-one (**1j**, $C_{16}H_{19}NO$)

Prepared by the general procedure[15,18] from 3,4-dimethyl-3-pyrrolin-2-one and 2,4,6-trimethylbenzaldehyde; m.p. 163-165°.

^{1}H-NMR (δ, $CDCl_3$): 6.85 (s, aromatic H), 6.65 (broad s, NH), 6.04 (sl. broad s, =CH—), 2.27 (s, aromatic CH_3-4), 2.15 (s, aromatic CH_3-2 and CH_3-6), 2.12 (sl. broad s, CH_3-4), 1.90 (sl. broad s, CH_3-3).

IR (cm^{-1}, KBr): 1690 (C=O).

MS (*m*/e, 70 eV): 241 (M^+, 61%), 227 (27%), 212 (base peak).

(Z)-3,4-Dimethyl-5-[4-methylphenyl(²H)methylene]-3-pyrrolin-2-one (*d*-**1e**, $C_{14}H_{14}{}^2HNO$)

A solution of 106.5 mg **1e** in 2 ml (²H)-trifluoroacetic was maintained 24 h at 60° (Ar atmosphere). Neutralisation with Na_2CO_3 saturated aqueous solution, extraction with $CHCl_3$ and evaporation to dryness afforded *d*-**1e** which was in all identical to a sample synthesized as described in[13]. The reversibility of the deuteration was followed by ¹H-NMR using a solution of trifluoracetic acid.

(Z)-3,4-Dimethyl-5-[aryl(²H)methylene]-3-pyrrolin-2-ones (*d*-**1a–k**); *General Procedure*

Except for *d*-**1e** described above, these compounds were only identified from their ¹H-NMR spectra recorded during the kinetic measurements. Under the conditions of the kinetics (see below), (²H) methylene derivatives were the unique reaction products, as confirmed for *d*-**1e**, *d*-**2e** and *d*-**3e** by thin layer chromatography and mass spectrometry.

Kinetic measurements for the deuteration reaction

0.2 *M* (²H)-Trifluoroacetic acid solutions of compounds **1a-k**, **2a** and **3e** in a resonance tube under argon atmosphere were warmed up to $60 \pm 1°$ and ¹H-NMR spectra were recorded. Each kinetic experiment was performed until a minimum of 80% disappearance of the methine proton signal. The apparent first order rate constants (k) were calculated by regresion analysis[22]; correlation coefficients (r) of about 0.98-0.99 were generally obtained; in no case they were below 0.94.

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