

Reactivity of Pyrrole Pigments, 4. Part¹: Deuteration of 5-Arylmethylene-3-pyrrolin-2-ones with d_1 -Trifluoroacetic Acid

Josep M. Ribó* and Francesc R. Trull

Departament de Química Orgànica, Facultat de Química, Universitat de
Barcelona, Barcelona-28-(Catalunya), Spain

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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

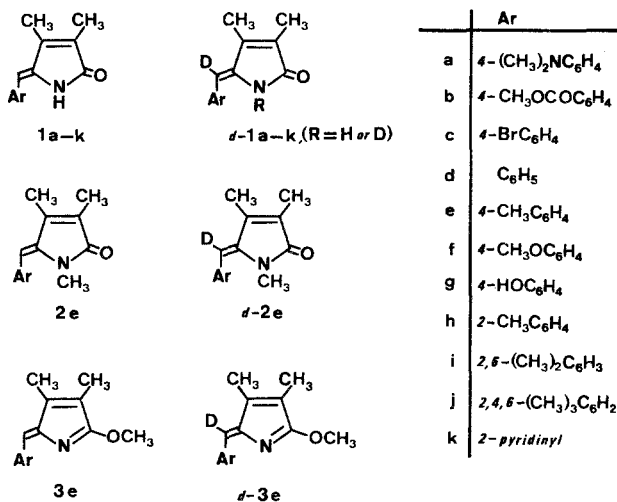
In a previous paper we described the reaction of 5-arylmethylene-3-pyrrolin-2-ones and pyrromethenones with cyanide ion to give the corresponding cyanomethylenepyrrolidin-2-ones². The site where this nucleophilic attack takes place is predicted by the reactivity indexes calculated from Fukui's frontier orbital model^{2,3}. The same model predicts that an electrophilic reagent will also attack at the bridge

carbon atom. In this paper we discuss the behaviour, of 5-arylmethylene-3,4-dimethyl-3-pyrrolin-2-ones, **1 a-k**, **2 e** and the lactim form of the last, **3 e** (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 **1 a-k**, **2 e** and **3 e** afford the corresponding products in which the hydrogen atom on the methylene bridge has been substituted by deuterium: d -**1 a-k**, d -**2 e** and d -**3 e** (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 **1 j**. 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 ($R=\text{CH}_3$) has a larger rate constant as **1e** ($R=\text{H}$) (see Table 1) according to the reaction path $A \rightarrow \text{Int}^+ \rightarrow B$. In contrast, the effect of a substituent at *para* position of the phenyl ring (for compounds **1a-g**) is

Scheme 2

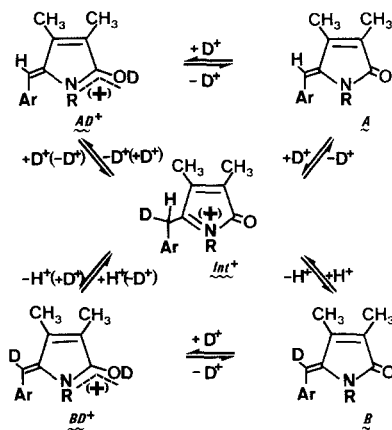


Table 1. Proton to deuterium exchange at the methine carbon of 5-ylidene-3-pyrrolin-2-ones (**1a-i**, **1k**, **2a** and **3a**); 0.2 M solutions in d_1 -TFA at 60°

Compound	Rate constant ^a $k \cdot 10^3 \text{ (s}^{-1}\text{)}$	$\log k_x/k_{1d}$
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 ¹H-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

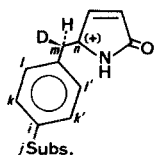
σ_R is calculated from $\sigma_R = \sigma_p - \sigma_I$ where σ_I accounts for the field effect of the substituent and σ_R for its total resonance contribution (i.e. $\sigma - \pi$, $n - \pi$ and $\pi - \pi$).

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}:

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

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 method⁸

	$1/r_{in}$	$0.9/r_{jn}$	$r_{k'n}$	r_{kn}	q_{im}	q_{ik} and $q_{ik'}$
<i>para</i> substitution	1/3.6	0.9/4.5	2.9	3.6	0.143	0.143
<i>ortho</i> 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	without the field effect contribution
<i>p</i> -CH ₃	-0.87	-0.91	-0.36	-0.23	-0.16
<i>o</i> -CH ₃	-0.87	-0.91	-0.36	-0.23	-0.16
<i>p</i> -Br	4.92	-1.14	-0.30	0.38	-0.19
<i>p</i> -OH	2.48	-3.70	-0.59	0.19	-0.58
<i>p</i> -OCH ₃	3.16	-3.14	-0.98	0.25	-0.54
<i>p</i> -COOR	3.18	0.93	0.49	0.25	0.18
<i>p</i> -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 method⁸ 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-pyrroline-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-pyrroline-2-one unit cannot be very large, since these two groups are not coplanar⁹. 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

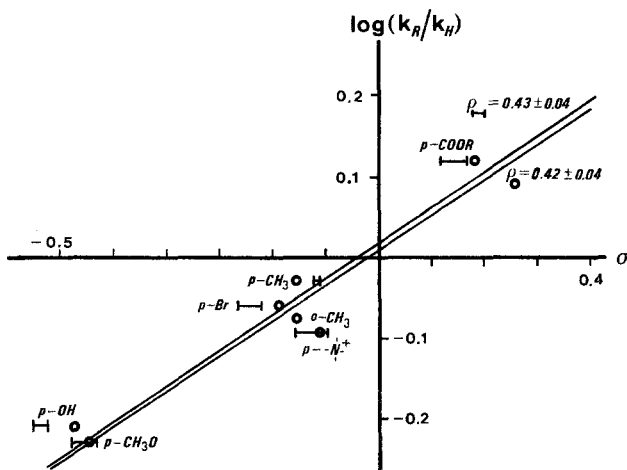


Fig. 1. Linear Free energy relationships for the deuteration of 5-arylmethylene-3-pyrrolin-2-ones **1a-i** and **1k**: —, σ_R ; $\circ$, σ (FMMF) without field effect contribution

reaction rate (regardless of the steric hindrance). This prediction is in fact confirmed as indicated by comparison of the reaction rates of **1e**, **1h** and **1i**. 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 **1a** and **1k**, 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 proposed¹¹ 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 HF₂₅₄ 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 (¹H-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**, C₁₅H₁₅NO₃)

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 H₂SO₄ 98%, were refluxed for 12 h. Neutralisation, evaporation of methanol and extraction of the aqueous phase with CHCl₃ afforded **1b** (463 mg; 34%); m.p. 219–221°.

¹H-NMR (δ, DCCl₃): 8.25 (broad, s, NH), 7.25 (m, aromatic H), 6.07 (slightly broad s, =CH—), 3.93 (s, CH₃O), 2.2 (sl. broad s, CH₃-4), 1.94 (sl. broad s, CH₃-3).

IR (cm⁻¹, KBr): 1710, 1690 (C=O).

(Z)-3,4-Dimethyl-5-(2,6-dimethylphenylmethylene)-3-pyrrolin-2-one
(**1i**, C₁₅H₁₇NO)

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-dimethylbenzonitrile¹⁹ with LiAlH(C₂H₅O)₃ according to the method described in^{20,21}]; m.p. 151–154°.

¹H-NMR (δ, CDCl₃): 7.05 (s, aromatic H), 6.62 (broad s, NH), 6.05 (sl. broad s, =CH—), 2.21 (s, two aromatic CH₃), 2.14 (sl. broad s, CH₃-4), 1.90 (sl. broad s, CH₃-3).

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**, C₁₆H₁₉NO)

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

¹H-NMR (δ, CDCl₃): 6.85 (s, aromatic H), 6.65 (broad s, NH), 6.04 (sl. broad s, =CH—), 2.27 (s, aromatic CH₃-4), 2.15 (s, aromatic CH₃-2 and CH₃-6), 2.12 (sl. broad s, CH₃-4), 1.90 (sl. broad s, CH₃-3).

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*, C₁₄H₁₄²HNO)

A solution of 106.5 mg **1e** in 2 ml (²H)-trifluoroacetic was maintained 24 h at 60° (Ar atmosphere). Neutralisation with Na₂CO₃ saturated aqueous solution, extraction with CHCl₃ and evaporation to dryness afforded *d-1e* which was in all identical to a sample synthesized as described in¹³. The reversibility of the deuteration was followed by ¹H-NMR using a solution of trifluoroacetic 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 ± 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 regression analysis²²; correlation coefficients (*r*) of about 0.98-0.99 were generally obtained; in no case they were below 0.94.

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