THE ARYL GROUP CONTROLS THE α/γ REGIOSELECTIVITY IN DEUTERATIONS OF 2-(p-SUBSTITUTED BENZYL)-4,6-DIMETHYLPYRYLIUM SALTS (1)

Alexandru T. Balaban, Mircea D. Gheorghiu and Teodor Silviu Balaban

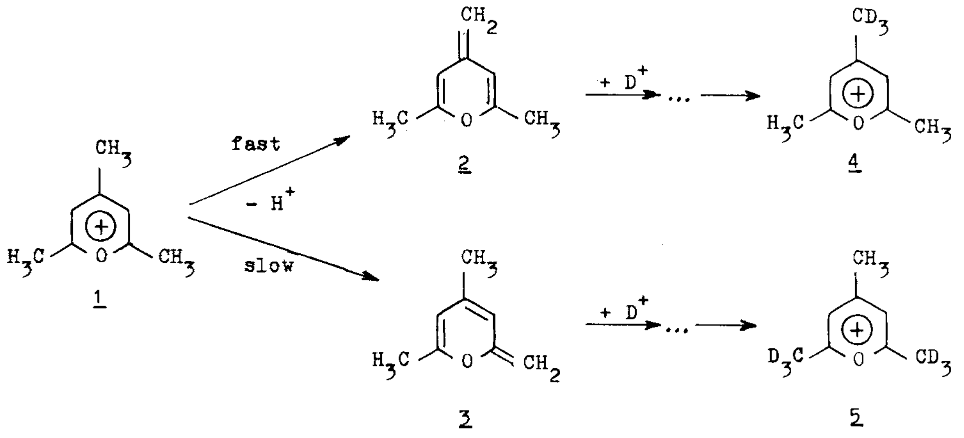
Polytechnic Institute, Department of Organic Chemistry,
Splaiul Independenţei 313, 76206 Bucharest, Roumania

SUMMARY

A kinetic study is reported for the deuteration (in sodium formate-containing HCOOD at 50 - 73°) of 2-benzyl-4,6-dimethylpyrylium perchlorate and of its derivatives possessing para-substituents at the phenyl ring (NO_2, Cl, Me, OMe). Intramolecular comparison of deuteration rates indicates that the 4-methyl is always deuterated 8-10 times faster than the 6-methyl ; however, the 2-methylene group is deuterated with a rate dictated by the nature of the aryl group : faster than the 4-methyl with p-NO_2 and p-Cl substituents, more slowly than the γ-methyl group with p-Me and p-OMe substituents. Hammett plots show good correlations for relative deuteration rates of the methylene group, and for ^{1}H-NMR chemical shifts for methyl and methylene protons.

INTRODUCTION

Previous papers have shown (2,3) that the high electronegativity of the positively-charged oxygen heteroatom in pyrylium salts 1 enables "benzylic" protons of α (2- , 6-) or γ (4-position) side-chains to undergo rapid isotope exchange in D_2O or CH_3-COOD. Since the exchange rate is enhanced on increasing the pH in the range 0 - 4, the reaction mechanism (3) involves deprotonation to anhydrobases (methylenepyrans) :



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Molecular orbital calculations (4) reveal that γ-methylenepyrans 2 have lower energies than α-methylenepyrans 3, explaining thus the higher deuteration rate of γ-methyl(ene) groups relative to α-methyl(ene) groups. Thus 2,4,6-trimethylpyrylium salts are deuterated in D_2O at 80 - 100° about ten times faster at the γ-methyl group (yielding 4) than at the α-methyl groups (when the result would have been 5, which cannot be obtained directly, but can be prepared by complete deuteration, followed by de-deuteration of the 4-methyl group).

This mechanism is supported by studies of the isotope effect (5), by the effect of varying the aryl group in deuterations of 2,6-diaryl-4-methylpyrylium (6), and by newer MNDO calculations (7).

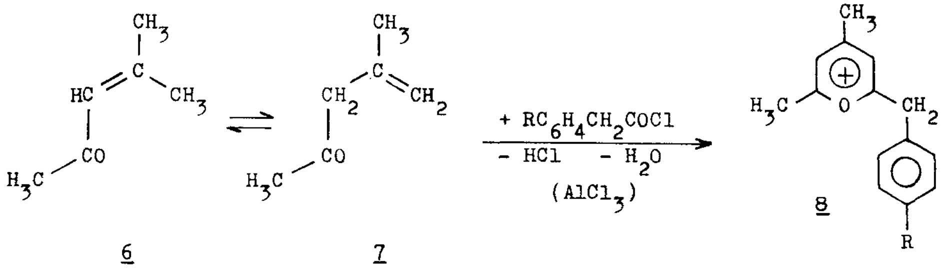
When an α-methylene group, as in 2-ethyl-4,6-dimethylpyrylium (8), or an α-methine group, as in 2-isopropyl-4,6-dimethylpyrylium (9) is compared intramolecularly to the α-methyl group, one finds that alkyl substitution at the exocyclic carbon atom of methylenepyrans exerts a slight stabilizing influence, leading to relative deuteration rates about twice higher for the α-methylene or α-methine group than for the α-methyl group.

The present paper reports a similar kinetic study of newly prepared 2-benzyl-4,6-dimethylpyrylium perchlorate and para-substituted derivatives thereof. One expects aryl groups bonded to the exocyclic carbon of methylenepyrans to exert a more pronounced conjugative stabilization than alkyl groups, which act only via the weaker inductive and hyperconjugative effects ; in addition, the nature of the para-substituent is expected to play a significant part in the deuteration rate of the corresponding methylene group. As it will be shown here, the experimental results fully bear out these expectations, providing thereby further support for the reaction mechanism.

KINETICS OF DEUTERATION

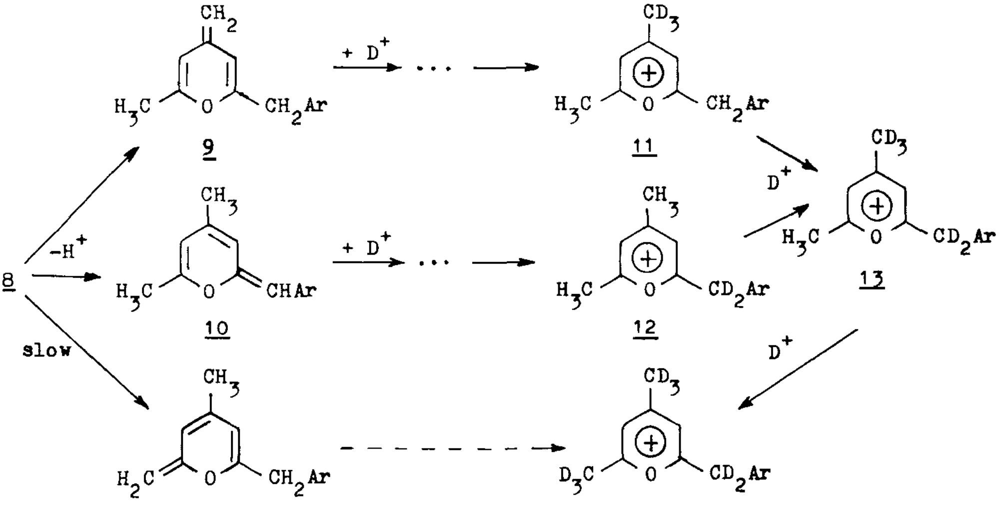
The deuteration of 2-benzyl-4,6-dimethylpyrylium perchlorate (8c, R = H) by isotope exchange in hydroxylic solvents can be followed by ^1H-NMR spectroscopy. However, the solubility in D_2O is too low even at reflux temperature ; CH_3-COOD cannot be employed because the methyl region is obscured by the solvent and we did not possess sufficiently pure (isotopically) CD_3-COOD ; therefore we prepared HCOOD, but we found that the rate of hydrogen exchange in pure HCOOD is too low for convenient kinetic determinations. Nevertheless we finally obtained satisfactory results with HCOOD containing sodium formate.

The newly prepared pyrylium salts 8 were obtained by acylation of mesityl oxide 6 which is known to contain at equilibrium about 20 % isomesityl oxide 7 ; the latter tautomer undergoes electrophilic substitution by $ArCH_2CO^+$ in the presence of anhydrous aluminium chloride, and the product is dehydrated yielding the pyrylium salt 8, isolated as the perchlorate.



	a	b	c	d	e
R =	NO_2	Cl	H	Me	OMe

Deuterations were carried out in the NMR vial which was thermostated at a convenient temperature in the range 50 - 73° for a specified time ; after chilling the vial, its ^{1}H-NMR spectrum was recorded, and four integral curves were registered, then the thermostating was resumed for another reading, monitoring the decrease of NMR peaks versus time. For those compounds which did not have non-exchangeable methyl groups, i. e. 8a, 8b and 8c, added 2,2-dimethyl-2-silapentane-5-sulfonate (DSS, sodium salt) was used as internal standard both for the zero point on the delta scale, and for the number of protons in order to provide a correction factor for any variation of the integrator sensitivity.



14

In order to minimize the errors, we decided to make only intramolecular rate comparisons, therefore it was not necessary to have exactly the same temperature and solvent composition for all five compounds. Thus it was possible to select the temperature of the thermostat so as to lead to convenient time intervals between recordings of NMR spectra. Since the temperature of the NMR instrument (around 25^o) was appreciably lower than that of the thermostat, deuterations during the recording of NMR spectra or during the cooling/reheating transitory periods were considered to be negligible.

The subtraction of the "background" due to DSS protons, and the calculation of rate values taking into account that the isotopic purity of the HCOOD + HCOONa solvent is 75 - 80 % is described in more detail in the subsequent paper in this series (10). The estimated error for relative rates is ± 10 % in Table 2.

Table 1 presents the ^{1}H-NMR data of the new pyrylium salts. Fortunately, all methyl(ene) peaks appear as well-separated singlets so that interpretations of integral curves are straightforward.

Table 1. ^{1}H-NMR chemical shifts (δ , ppm) of pyrylium salts <u>8</u> in trifluoroacetic acid

Comp.	R	2-CH_2 (α)	6-CH_3 (α)	4-CH_3 (γ)	Other CH_3	3-CH (β)	5-CH (β)	Aromatic
a	NO_2	4.70	2.97	2.80	-	*	*	7.70 , 8.40 **
b	Cl	4.52	2.96	2.78	-	7.82	7.68	7.43
c	H	4.50	2.95	2.73	-	7.73	7.58	7.42
d	Me	4.47	2.93	2.73	2.37	7.73	7.60	7.25
e	OMe	4.40	2.90	2.68	3.97	7.73	7.60	7.33 , 7.08 **

* Obscured by aromatic protons.

** Coupling constant for pseudo-AB multiplet J = 8 Hz.

According to expectations, the NMR data presented in Table 1 indicate that the α-CH_2 chemical shift δ is strongly dependent on the nature of the <u>para</u>-substituent R. A Hammett plot (substituent σ constants will be found in Table 2) shows a linear correlation between δ and σ . By contrast, the chemical shifts of the 4-CH_3 and 6-CH_3 groups are much less affected, as shown in Figure 1.

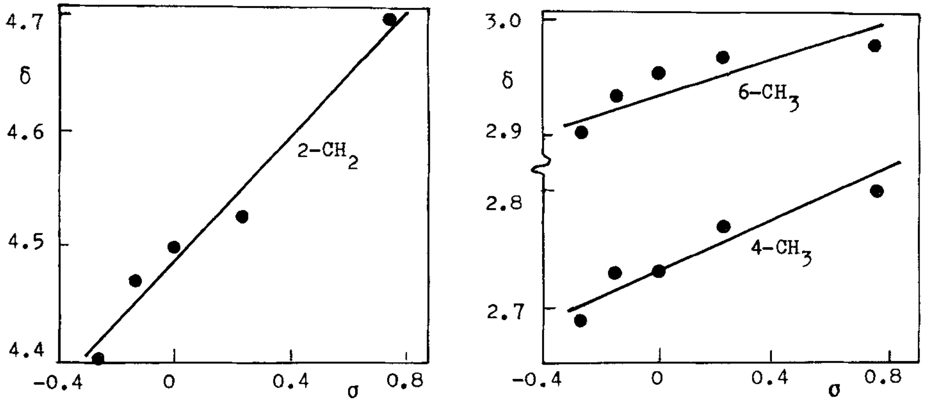


Fig. 1. Hammett plot of chemical shifts for pyrylium salts 8

RESULTS AND DISCUSSION

It can be expected that, while with aliphatic substituents the γ-methylenepyran 2 is much more stable than α-methylenepyrans 3, the introduction of conjugated aryl groups ought to make the isomeric anhydrobases 9 and 10 of comparable stability, depending on the *para*-substituent R. Indeed, as shown in Table 2, the relative deuteration rates of γ-CH_3 and α-CH_2 groups in the unsubstituted compound 8c and the *para*-methyl derivative 8d are fairly similar.

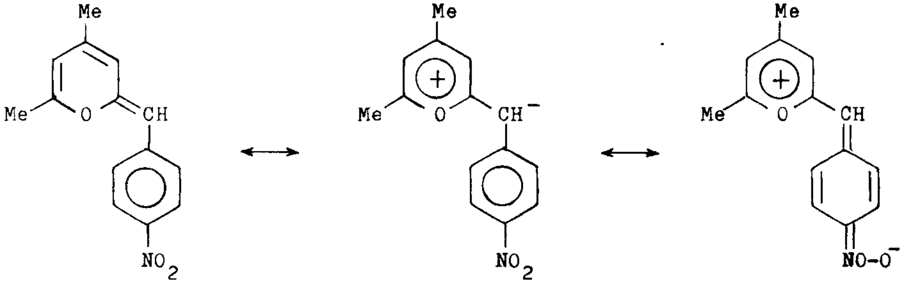
Since the α-CH_3 group is deuterated with the lowest rate, for intramolecular comparisons we calculate deuteration rates relatively to this group in Table 2, assigning arbitrarily relative rate 1 to this 6-methyl group.

It can also be expected that the nature of the aryl group will have a marked influence on the deuteration rate of the α-methylene group, and that the rates of the α- and γ-methyl groups will not be appreciably affected. Table 2 shows, indeed, that if the α-CH_3 group has by convention the relative rate 1, the experimentally found relative rate of the γ-CH_3 group is almost constant (within experimental errors, relative rates 8 - 10, as in trimethylpyrylium 1).

The data concerning the relative deuteration rate of the α-methylene group in 8 are the most interesting. This rate increases by almost one order of magnitude when the *para*-substituent varies from methoxy to nitro, *reverting the α/γ regioselectivity*. Table 2 shows that electron-acceptor substituents R (Cl, NO_2) markedly increase the deuteration rate by acidifying the methylene protons and by stabilizing the methylenepyran as indicated in formula 10a. Electron-donating groups, on the other hand, exert the opposite effect.

Table 2. Relative deuteration rates of 8 in HCOOD + HCOONa

Comp.	R	Hammett σ	Temp. °C	6-CH_3 (α)	4-CH_3 (γ)	2-CH_2 (α)	Ratio $\frac{4-}{2-}$
a	NO_2	+ 0.78	50	1	10	60	0.17
b	Cl	+ 0.23	57	1	8	14	0.57
c	H	0	70	1	9	10	0.90
d	Me	- 0.17	70	1	8	7	1.14
e	OMe	- 0.27	73	1	10	7	1.43



10a

Figure 2 presents the Hammett plot of the ratio between the relative rates of deuteration in the positions 4 and 2. Since this ratio crosses the value 1, these data illustrate again the interesting regioreversed α/γ selectivity in deuterations of appropriately-substituted pyrylium salts 8.

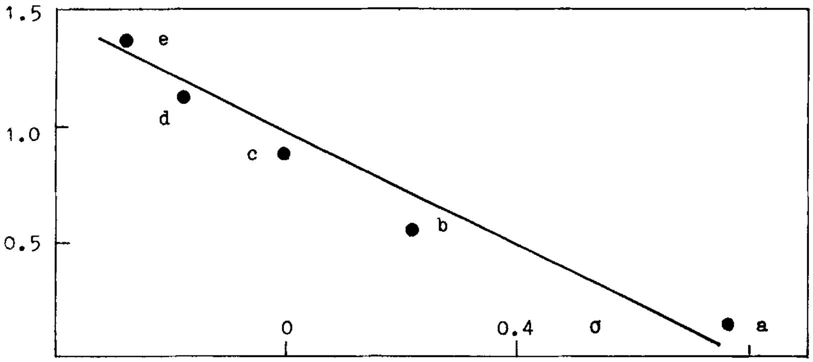


Fig. 2. Hammett plot of the ratio of relative rates (4-/2-)

In conclusion, we have evidenced that the α-CH_2/γ-CH_3 regioselectivity of deuteration kinetics for pyrylium salts 8 is controlled by the nature of the aryl group, which may cause even a reversal of the normal regioselectivity when electron-acceptor are present as substituents of the aryl group ; in this case, the α-methylene group undergoes faster deuteration than the γ-methyl group.

EXPERIMENTAL

^{1}H-NMR Spectra were recorded with a 60 MHz Varian EM-360L instrument.

Preparation of HCOOD. Commercial 98-100 % formic acid (25 ml, 30.5 g, 665 mmol) was equilibrated with 5 ml of 99.8 % deuterium oxide (250 mmol). Freshly sublimed phthalic anhydride (100 g) was added, and the mixture was refluxed for one hour, then formic acid (b.p. 101-105°) was distilled off at normal pressure (yield 21 g, deuteration at carboxyl about 40 %). The operation was repeated three times with 5 ml portions of fresh D_2O for each equilibration, affording 15 ml HCOOD containing 75-80 % deuterated carboxyl. This procedure is an adaptation of the method for obtaining anhydrous formic acid from 80 % formic acid (11).

Sodium formate, prepared from sodium hydroxide (concentrated aqueous solution) and a slight excess of formic acid, was anhydrized at 200° in an oven for 4 hrs. Then a small amount of deuterium oxide was added for obtaining a saturated solution at the boiling temperature, and the product was calcined again at 200° for 3 hrs.

For kinetic measurements, the NMR vial contains about equal molar amounts of pyrylium salt and sodium formate. When the reactions are faster, e.g. for 8a, less sodium formate can be added.

Preparation of pyrylium salts 8. Powdered anhydrous aluminium chloride (1 mol) was introduced into a stirred ice-cooled solution of arylacetyl chloride (1.5 mol) in carbon disulfide. After completion of the addition, mesityl oxide (1 mol) was added dropwise with cooling, and the stirring was continued at room temperature for 3 hours, then the mixture was left overnight. The mixture was decomposed by pouring it on ice and hydrochloric acid ; the aqueous layer was extracted with ethyl ether for removing water-insoluble products, and was then separated and treated with perchloric acid till precipitation was complete. After standing in the refrigerator for several hours, the pyrylium perchlorates crystallized in most cases and were filtered off. Yields 3 - 7 % after recrystallization from water, or aqueous acetic acid. The pyrylium salts afforded satisfactory elemental analyses.

2-Benzyl-4,6-dimethylpyrylium perchlorate (8c, R = H), m.p.110° (water).

2-p-Methylbenzyl-4,6-dimethylpyrylium perchlorate (8d, R = Me), m.p. 80 - 85°, crystallized slowly ; recrystallization from water or from acetic acid and ethyl ether yielded oily products which crystallized slowly on seeding.

2-p-Methoxybenzyl-4,6-dimethylpyrylium perchlorate (8e, R = OMe), m. p. 147° (from water).

2-p-Nitrobenzyl-4,6-dimethylpyrylium perchlorate (8a, R = NO_2), m. p. 159° (from aqueous acetic acid).

2-p-Chlorobenzyl-4,6-dimethylpyrylium perchlorate (8b, R = Cl) did not crystallize, but the oily product afforded a clear ^{1}H-NMR spectrum, free of any detectable impurity.

For further characterization, treatment of the unsubstituted perchlorate 8c with ethanolic methylamine, followed after 15 min. by precipitation with ethyl ether, afforded the crystalline 2-benzyl-1,4,6-trimethylpyridinium perchlorate, m.p. 122° (from water). Its ^{1}H-NMR spectrum in F_3C-COOH has peaks at δ = 4.48 (2H, s, 2-CH_2), 4.11 (3H, s, N-CH_3), 2.83 (3H, s, 6-CH_3) and 2.61 (3H, s, 4-CH_3) in addition to seven aromatic and pyridinium protons as multiplet at 7.0 - 7.8 ppm.

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* Note : a correction of one literature quotation should be made in J. Labelled Comp. Radiopharm. 18 : 1621 (1981), namely ref. 22 in that paper should read :
Gârd, E., Stănoiu, I.I., Balaban, A.T. and Chiraleu, F.- Rev. Roumaine Chim. 14 : 247 (1969).

Note for the experimental part : the low yield in the preparation of pyrylium salts 8 may be due to self-acylation of the arylacetyl chloride when the reaction is carried out with the pre-formed $ArCH_2COCl.AlCl_3$ complex. Improved yields (7-10 %) are obtained if the solution of the arylacetyl chloride and mesityl oxide in carbon disulfide is added dropwise into a suspension of ahnydrous aluminium chloride in carbon disulfide.