REGIOSELECTIVE DEUTERATION KINETICS OF 2,3,6-TRIMETHYL-4-PHENYLPYRYLIUM AND 2,6-DIMETHYL-3,4-DIPHENYLPYRYLIUM SALTS (1)

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SUMMARY

The deuteration of 2,3,6-trimethyl-4-phenylpyrylium salts in D_2O + D_3CCN indicates that the 2-methyl group is deuterated 3.3 times faster than the 6-methyl group. The ^1H-NMR assignment is based on an unambiguous synthesis of the 2-CD_3-congener ; similar assignments were made for 2,3,6-trimethyl-4-phenylpyridine, and lanthanide-induced shifts were determined. The deuteration of 2,6-dimethyl-3,4-diphenylpyrylium perchlorate in anhydrous HCOOD + NaOOCH (the assignment in ^1H-NMR spectra is straightforward owing to the shielding of 2-methyl protons by the neighbouring orthogonal phenyl group) indicates similarly that the 2-methyl group is deuterated 3.0 times faster than the 6-methyl group. Though the relative rates for 2- and 6-methyl groups do not differ sufficiently for preparative regioselective deuterations, the present findings raise interesting problems for M.O. calculations.

INTRODUCTION

The deuteration of "benzylic" hydrogens in α or γ positions of pyrylium salts by isotopic exchange in hydroxylic solvents was reviewed (2,3). The deuteration kinetics of symmetrically-substituted pyrylium salts has been studied in several preceding parts of this series ; it was found (4,5) that γ-methyl protons exchange about ten times faster than α-methyl protons, a result of preparative value for regioselective deuteration (6). Earlier kinetic studies have also compared α-methyl with α-ethyl (7), or α-isopropyl groups (8) in this reaction for unsymmetrically-substituted pyrylium salts. Recently (9) it was observed that there is a marked difference in deuteration rates between two α-methyl groups (in positions 2 and 6) if the pyrylium salt is unsymmetrically substituted by having a substituent in position 3 : thus 2,3,4,6-tetramethylpyrylium (1) and 2,4,6-trimethyl-3-phenylpyrylium (2) afforded rela-

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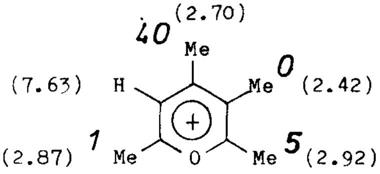
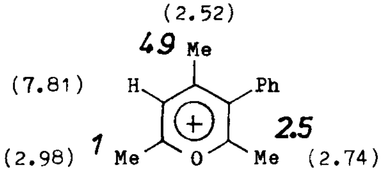
tive deuteration rates indicated by the larger figures without brackets in the formulas, while chemical shifts (δ , in trifluoroacetic acid) are in brackets. The solvent for isotopic exchange is indicated under the formulas.





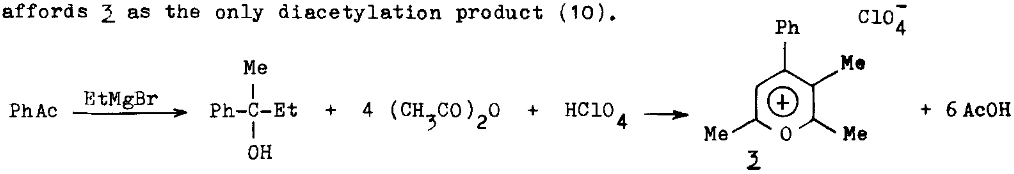
Deuteration in : D_2O D_2O (45 %) + D_3COD (55 %)

1 2

As indicated above, similarly to symetrically-substituted pyrylium salts, the γ -methyl is deuterated fastest, but there is also a marked difference between the 2-methyl which is deuterated faster, and the 6-methyl when there exists a substituent in position 3 ; the assignment of ^{1}H-NMR peaks for 1 was based on an unambiguous synthesis of the 6-deuterated 1 (9). For 2 the ^{1}H-NMR assignment was straightforward owing to the shielding exerted by the non-coplanar 3-phenyl on the 2- and 4-methyl protons (but not on the remote 6-methyl protons). It should be noted that the 2-methyl protons of 1 resonate at lower field than the 6-methyl protons.

DEUTERATION KINETICS OF 2,3,6-TRIMETHYL-4-PHENYLPYRYLIUM PERCHLORATE

The present paper reports the kinetic study of deuteration for 2,3,6-trimethyl-4-phenylpyrylium perchlorate (3). This salt was prepared as described earlier by diacetylation of ethyl-methyl-phenyl-carbinol (2-phenyl-2-butanol) which undergoes dehydration in situ affording a mixture of 2-phenyl-1- and -2-butenes ; with acetic anhydride and perchloric acid, this olefin mixture affords 3 as the only diacetylation product (10).



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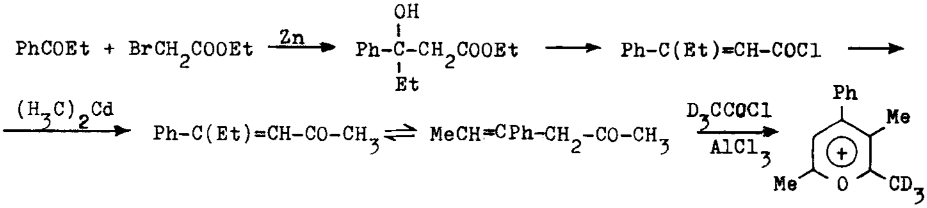
The previous paper (10) reported that in refluxing deuterium oxide the β -methyl does not undergo deuteration, the β -proton in position 5 is deuterated very slowly (probably via the ring-opened pseudobase), while the α -methyl protons underwent deuteration ; at that time it was not attempted to follow kinetically the deuteration of 2- and 6-methyl groups separately.

Since the solubility of 3 in water is rather low even at reflux, the deuteration was now carried out in a mixture of deuterium oxide with anhydrous deuterated acetonitrile (1 : 2 vol.). The two α-methyl peaks appear at slightly different fields, sufficiently separated at sweep width 50 Hz for meaningful integrated curves in the kinetic study. The assignment of the two α-methyl peaks was effected by unambiguous synthesis of 2-deuteromethyl-3,6-dimethyl-4-phenylpyrylium according to the following reactions :



$$\mathrm{PhCOEt + BrCH_2COOEt \xrightarrow{Zn} Ph\text{-}\underset{Et}{\overset{OH}{C}}\text{-}CH_2COOEt \longrightarrow Ph\text{-}C(Et){=}CH\text{-}COCl \longrightarrow}$$

$$\mathrm{\xrightarrow{(H_3C)_2Cd} Ph\text{-}C(Et){=}CH\text{-}CO\text{-}CH_3 \rightleftharpoons MeCH{=}CPh\text{-}CH_2\text{-}CO\text{-}CH_3 \xrightarrow[AlCl_3]{D_3CCOCl}}$$

Similarly to 1, in the case of 3 the 2-methyl protons are found to resonate at lower field than the 6-methyl protons, by the intensity difference of the α-methyl peaks in 3-(2-d_3)

Conversion of pyrylium salts into the corresponding pyridines under the action of ammonia allows correlations to be made with the chemical shifts of these pyridines and with their molar indiced shifts in the presence of europium chelates. Table 1 presents these ^{1}H-NMR data.

Kinetic determinations were carried out at 74°C. Results are presented in Table 2. Relative deuteration rates were obtained from pseudo-first order straight lines in semilogarithmic representation versus time. The result indicates that in the pyrylium salt 3, the 2-methyl group undergoes faster deuteration (3.3 times) than the 6-methyl group.

The corresponding pyridine 4 has the α-methyl ^{1}H-NMR peaks in the same order. This was checked as indicated above by converting 3-(2-d_3) synthesized unambiguously into the corresponding 4-(2-d_3) and recording its NMR spectrum. Comparison of NMR data for the pyridines 1A and 4 in Table 1 indicates a close parallelism : the 2-methyl group appears at lower field and has a lower molar induced shift in the presence of europium chelates, Eu(fod)$_3$-d_{27}. As in the case of 1A, we assume that the latter finding indicates a non-symmetric co-ordination between the europium chelate and the lone electron pair of the pyridine 4, as shown in formula 4A. Such non-symmetric co-ordination may be due to the buttressing of the 2-methyl by the geared 3-methyl group, while methyl 6 is free.

Table 1. ^{1}H-NMR data of pyrylium salts and pyridines (ppm)

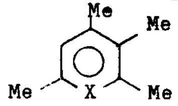
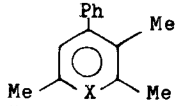
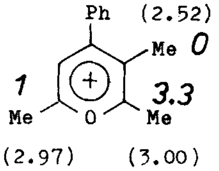
Compound							
		$\underline{1}$, X = O^+	$\underline{1A}$, X = N		$\underline{3}$, X = O^+	$\underline{4}$, X = N	
Solvent		F_3C-COOH	CS_2	CCl_4	F_3C-COOH	$CDCl_3$	CCl_4
Chemical shift δ	2-Me	2.92	2.36	2.39	3.00	2.56	2.40
	3-Me	2.42	2.02	2.12	2.52	2.14	2.07
	4-Me	2.70	2.12	2.17	-	-	-
	5-H	7.63	6.64	6.65	7.76	6.87	6.68
	6-Me	2.87	2.30	2.34	2.97	2.50	2.38
Molar induced shift	2-Me	-	13.0	-	-	10.7	-
	3-Me	-	3.7	-	-	4.0	-
	4-Me	-	3.7	-	-	-	-
	5-H	-	7.9	-	-	5.8	-
	6-Me	-	14.7	-	-	13.0	-
References		(9)	(11)	(9)	Present paper		

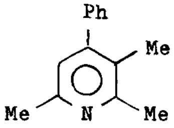
Table 2. Kinetics of the deuteration of 2,3,6-trimethyl-4-phenylpyrylium perchlorate (in D_2O / D_3CCN, 33 / 67 vol.%) at 74°C [a]

Time min.	2-Methyl = a		6-Methyl = a'		3-Methyl = b
	mm	$\ln(ab_o/b)$	mm	$\ln(a'b_o/b)$	mm
0	63	4.14	64	4.16	58 = b_o
3	38	3.64	57	4.02	59
6	26	3.13	55	3.88	66
9	16	2.58	47	3.66	70
15	13	2.40	35	3.40	68

[a] Each value a, a', b (in mm) is the average of four integral curves. The integral heights corresponding to peak areas in the NMR spectra differ by at most 2 mm between individual curves. The non-deuterable 3-methyl peak serves as internal standard for the number of protons.



$\underline{3}$



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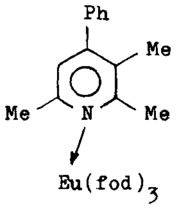
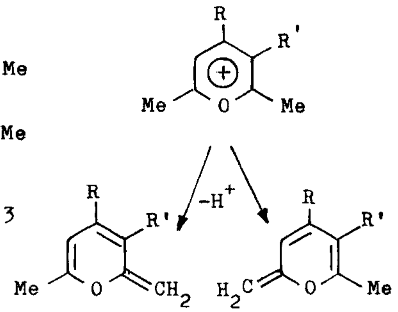


$\underline{4A}$

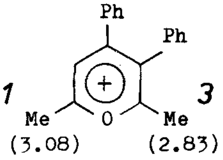


$\underline{6}$ $\underline{7}$

DEUTERATION KINETICS OF 2,6-DIMETHYL-3,4-DIPHENYLPYRYLIUM PERCHLORATE

In order to investigate an unsymmetrically-substituted system derived from 2,6-dimethyl-4-phenylpyrylium with an unambiguous assignment of the 2- and 6-methyl peaks in the ^{1}H-NMR spectrum without resorting to singly-deuterated compounds obtained by synthesis, 2,6-dimethyl-3,4-diphenylpyrylium perchlorate (5) was selected : in this case the 3-phenyl group which is practically orthogonal to the pyrylium ring shields the 2-methyl appreciably (chemical shifts are indicated on the formula in brackets ; the solvent is HCOOD and the internal standard is DSS, see below).

On the other hand, with the introduction of a second phenyl group the solubility of pyrylium perchlorates decreases so much that mixtures of D_2O with organic solvents are no longer satisfactory. Only carboxyl-deuterated acids are able to function both as solvents and as sources of deuterium for the isotopic exchange. In a previous paper, it was shown (12) that CH_3COOD (easily available from $Ac_2O + D_2O$) is a good agent for this purpose in preparative reactions, though the exchange rate is lower than in D_2O : the lower pK_a slows down the deprotonation to methylenepyrans. However, for kinetics by ^{1}H-NMR, CH_3COOD is unsuitable because the methyl region is obscured by the solvent. We therefore prepared HCOOD which is a good solvent, but since it is an appreciably stronger acid than acetic acid, no deuteration is observed at all in it at 90°. Only on addition of anhydrous sodium formate was it possible to obtain a satisfactory kinetic curve.



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The kinetic determinations were carried out by heating at 70° the solution of 5 in HCOOD + HCOONa for a definite time in the NMR vial, chilling it, recording the NMR spectrum at room temperature, and repeating this process several times. The recorded spectrum consists in four integral curves. The internal standard which does not undergo deuteration is sodium 2,2-dimethyl-2-silapentane-5-sulfonate (Tier's salt, DSS) and it serves both as zero on the delta scale, and for the number of protons, by correcting the sensitivity of the integrator through the factor s_0/s like b_0/b in Table 2.

Unlike the previous experiments with 1 - 3 (in which owing to the large excess of practically 100 % deuterated solvent, the equilibrium composition of methyl groups was practically CD_3) in the present case the isotopic purity of HCOOD (prepared via three equilibrations with limited amounts of D_2O followed each time by refluxation with phthalic anhydride and distillation) was about 75 %, as indicated by the relative areas of the two CH and OH peaks in the ^{1}H-NMR spectrum of the mixture HCOOD + HCOONa + DSS recorded initially, before dissolving the pyrylium salt. This fact has to be taken into account in the analysis of kinetic data, because in the present case the peak intensity at equilibrium no longer decreases to zero.

According to the isotopic exchange law, the rate is the slope of the pseudo-first order straight line obtained by plotting $\ln(a_c - a_{c,inf})$, (where the corrected peak area a_c is as_0/s, and the equilibrium value $a_{c,inf}$ is 25 % of the initial peak intensity, or corrected area) versus time. Since the internal DSS standard compound has a small "background" due to the $(CH_2)_3$ protons, this background has to be subtracted from the integral curves for each point of the kinetic plot. With all these corrections, and with eight points of the plot at 0, 4, 7, 14, 28, 43, 63, and 83 minutes of heating at 70^0 (when the 2-methyl peak almost reaches equilibrium, but the 6-methyl peak decreases by almost half) one finds that the slope ratio for deuteration at the 2- and 6-methyl groups is 3.0. Thus the 2-methyl group of 2.6-dimethyl-3,4-diphenylpyrylium undergoes deuteration three times faster than the 6-methyl group.

CONCLUSION

It was found that the unsymmetrically 2,3,4,6-tetrasubstituted pyrylium salts exchange protons at α-positions with different rates. On introducing into the 2,6-dimethyl-4-phenylpyrylium structure a 3-methyl group to afford 3, the 2-methyl protons are deshielded by 0.03 ppm and undergo deuterium exchange 3.3 times faster relatively to the 6-methyl protons. The assignment of 2- and 6-methyl proton peaks in the ^{1}H-NMR spectrum of 3 was effected by synthesis of authentic 2-deuteromethyl-3,6-dimethyl-4-phenylpyrylium perchlorate. On introducing into the same 2,6-dimethyl-4-phenylpyrylium structure a 3-phenyl group to afford 5, it was found that the 2-methyl protons undergo deuterium exchange 3 times faster than the 6-methyl protons.

By comparing the ^{1}H-NMR chemical shifts of pyrylium salts 1 and 3, differing by replacing the 4-methyl group of 1 by a phenyl, it may be seen that all methyl chemical shifts of 3 are moved downfield with 0.09 ± 0.01 ppm relatively to the corresponding ones in 1. Similarly, by comparing 2 with 5 one observes that the analogous replacement of a 4-methyl by a 4-phenyl causes all remaining corresponding methyl chemical shifts to move downfield with 0.10 ± 0.01 ppm.

In all four cases so far investigated (1, 2, 3, and 5) the 2-methyl protons in 3,4-disubstituted-2,6-dimethylpyrylium salts exchange faster than the 6-methyl protons. Theoretical calculations using the MNDO method show indeed (13) that the corresponding anhydrobases (methylenepyrans) have energies indicating that for R = R' = Me 6 is more stable than 7, therefore deprotonation will occur more readily at position 2 than at position 6 in a thermodynamically-controlled process.

EXPERIMENTAL

The ^{1}H-NMR spectra were recorded with an A-60A or an EM-360L Varian spectrometer. Kinetic determinations were performed by heating for the prescribed time in a thermostat the ^{1}H-NMR vial, then chilling it in ice-water and recording the NMR spectrum and at least four integral curves at room temperature. The process is then repeated for the next reading.

2,3,6-Trimethyl-4-phenylpyrylium perchlorate (3). The reaction of 2-phenyl-2-butanol with excess acetic anhydride and perchloric acid afforded the pyrylium perchlorate 3 according to the procedure described earlier (10).

Preparation of 2-deuteromethyl-3,6-dimethyl-4-phenylpyrylium perchlorate 3-(2-d_3). Acetic acid-d_3 was prepared from malonic acid as described (9). By distillation with benzoyl chloride it was converted into D_3C-COCl. The Reformatsky reaction of propiophenone with ethyl bromoacetate in the presence of zinc powder (14) yielded the liquid hydroxy-ester which was hydrolyzed under reflux with sodium hydroxide in aqueous methanol. Subsequent dehydration with cold (-10°) 98 % sulfuric acid yielded in 20 min. a homogeneous red (fluorescent in green) solution which on dilution with ice-water yielded β-ethylcinnamic acid (15), in overall yield relative to propiophenone 60 %. The acid was converted into the acid chloride with excess thionyl chloride, and after removing the excess of $SOCl_2$ under vacuum, the residue was treated with a benzene solution of dimethylcadmium in stoichiometric amount. The resulting ketone mixture was distilled at 118° /2 Torr, yield 55 %. It contains according to GLC and IR data comparable amounts of α,β-unsaturated ketone (4-phenyl-3-hexene-2-one) and β,γ-unsaturated ketone (4-phenyl-4-hexene-2-one). By contrast, the yield reported when dimethylzinc was used instead of dimethylcadmium amounted only to 20 % (16).

This ketone mixture, admixed with a 20 % molar excess of D_3C-COCl and carbon disulfide was introduced dropwise into a stirred ice-cool suspension of anhydrous aluminium chloride in carbon disulfide. The violet, then black, mixture was stirred at room temperature for four hours and was left overnight. Then decomposition with ice and hydrochloric acid of the solid complex after decanting the carbon disulfide layer, followed by extraction with ethyl ether and treatment of the aqueous layer with perchloric acid afforded in 10 % yield 3-(2-d_3). If the ketone mixture is introduced into a preformed complex of acetyl chloride and aluminium chloride in carbon disulfide, a different perchlorate is obtained, as will be reported separately.

Preparation of 2,6-dimethyl-3,4-diphenylpyrylium perchlorate (5). According to literature data (17), diacetylation of 1,2-diphenylpropene yielded 5.

Anhydrous HCOOD and HCOONa were prepared as described earlier (1).

REFERENCES

1. Preceding part, foregoing paper. The present paper is Part XVI in the series.
2. Balaban, A.T.- J.Labelled Comp.Radiopharm. 18 : 1621 (1981).
3. Balaban, A.T., Dinculescu, A., Dorofeenko, G.N., Fischer, G.W., Koblik, A.V., Mezheritskii, V.V. and Schroth, W.- Pyrylium Salts. Preparation, Reactions and Physical Properties (Adv. Heterocyclic Chem. Suppl. Vol. 2), ed. Katritzky, A.R., Academic Press, New York, 1982, p. 62.
4. Gard, E., Vasilescu, A., Mateescu, G.D. and Balaban, A.T.- J.Labelled Comp. 3 : 119 (1967).
5. Gârd, E., Stănoiu, I., Chiraleu, F. and Balaban,A.T.- Rev. Roumaine Chim. 18 : 257 (1973).
6. Balaban, A.T.-Steric versus electronic effects of deuterium, in Synthesis and Applications of Isotopically Labeled Compounds, eds. Duncan, W.P. and Susan A.B., Elsevier, 1983, p. 237, Amsterdam.
7. Stănoiu, I.I., Gârd, E., Uncuţa, C., Chiraleu, F., and Balaban, A.T.- Rev. Roumaine Chim. 24 : 209 (1979).
8. Idem, ibid. 22 : 1359 (1977).
9. Balaban, A.T., Uncuţa, C., and Chiraleu,F.-J.Labelled Comp. Radiopharm. 19 : 783 (1982).
10. Gârd, E., Stănoiu, I., Balaban, A.T. and Chiraleu, F.- Rev. Roumaine Chim. 14, 247 (1969).
11. Balaban, A.T., Bota, A., Chiraleu, F., Sliam, E., Haneş, A. and Drăghici, C.- Rev. Roumaine Chim. 22 : 1003 (1977).
12. Gârd, E., Bally, E., Vasilescu, A., Arsene, A., and Balaban, A.T.- J. Labelled Comp. 1 : 182 (1965).
13. Paper to be published in collaboration with P.v.R.Schleyer and D.Wilhelm.
14. Barltrop, J.A., Acheson, D.M., Philipott, P.G., MacPhee, K.E. and Hunt, G.S.- J. Chem. Soc. 2928 (1956).
15. Stoermer,R., Grimm,F. and Laage,E.- Ber.dtsch.chem.Ges.50 : 959 (1917).
16. Johnson,J.D.A., and Kon,G.A.R.- J. Chem. Soc. 2758 (1926).
17. Balaban,A.T. and Nenitzescu,C.D.- Liebigs Ann.Chem. 625 : 74 (1959).